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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

AMGEN, INC. Plaintiff, v. SANDOZ INC., et al. Defendants.	**Civil Action No. 18-11026 (MAS)(DEA) (consolidated)** [redacted]

DEFENDANTS' PROPOSED CONCLUSIONS OF LAW

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TABLE OF ABBREVIATIONS

Term	Definition
’358 patent	U.S. Patent No. 6,020,358
’638 patent	U.S. Patent No. 7,427,638
’536 patent	U.S. Patent No. 8,455,536
’101 patent	U.S. Patent No. 7,893,101
’283 patent	U.S. Patent No. 8,093,283
’541 patent	U.S. Patent No. 10,092,541
’515 application	U.S. Provisional Application No. 60/366,515
’052 publication	U.S. Patent Publication No. 2003/0187052
Amgen	Plaintiff Amgen Inc.
ANDA	Abbreviated New Drug Application
API	Active Pharmaceutical Ingredient
Apremilast	(+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione
Brittain 1997	Brittain, H.G., “Spectral Methods for the Characterization of Polymorphs and Solvates,” *Journal of Pharmaceutical Sciences* (1997)
Brittain 1999	H.G. Brittain, *Methods for the Characterization of Polymorphs*, Polymorphism in Pharmaceutical Solids, part of the Drugs and the Pharmaceutical Sciences collection, Vol. 95, pp. 227-278 (H. Brittain ed., 1999)
Byrn 1994	S.R. Byrn et al., Solid-State Pharmaceutical Chemistry, Chem. Mater. 6:1148-1158 (1994)
Byrn 1995	S. R. Byrn et al., “Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations,” *Journal Pharmaceutical Research*, 12(7): 945-54 (1995)
cAMP	Adenosine 3′,5′-cyclic monophosphate
Celgene	Celgene Corp.

Term	Definition
DDX	Defendants' demonstratives
DDX-ZYDUS	Defendant Zydus' demonstratives
Defendants	Defendants Sandoz Inc., and Zydus Pharmaceuticals (USA) Inc.
DFF	Defendants' proposed findings of fact
DSC	Differential scanning calorimetry
DTC	Direct to consumer
DTX	Defendants' trial exhibit
DVS	Dynamic vapor sorption
Dyke 1999	Dyke et al., "The therapeutic potential of PDE4 inhibitors," *Expert Opin. Invest. Drugs*, 8(9): 1301-25 (1999)
EPO	European Patent Office
FDA	U.S. Food and Drug Administration
Fieser	Louis F. Fieser & Kenneth L. Williamson, *Crystallization*, *in* Organic Experiments, pp. 43-53 (3rd ed. 1975)
Guillory	J. K. Guillory, *Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids*, Polymorphism in Pharmaceutical Solids, part of the Drugs and the Pharmaceutical Sciences collection, Vol. 95, pp. 183-226 (H. Brittain ed., 1999)
Haleblian	John Haleblian & Walter McCrone, Pharmaceutical Applications of Polymorphism, *J. Pharm. Sci.* 58:911 (1969)
ICH 1994	ICH Harmonised Tripartite Guideline, Dose-Response Information to Support Drug Registration (Mar. 10, 1994)
ICH Guidelines	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (1999)
IMiDs	immunomodulatory drugs
JTX	Joint trial exhibit

Term	Definition
Kavanaugh 2014	Kavanaugh et al., "Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor," *Ann. Rheum. Dis.*, 73: 1020-26 (2014)
LPS	Lipopolysaccharide
Marriott 2001	Marriott et al., "Immunotherapeutic and antitumor potential of thalidomide analogues," *Expert Opinion on Biological Therapy*, 1(4): 675-82 (2001)
Muller 1998	Muller et al., "Thalidomide Analogs and PDE4 Inhibition," *Bioorganic & Medicinal Chemistry*, 8: 2669-74 (1998)
NCT '092	Clinical Trial No. NCT00456092, "A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Efficacy and Safety Study of CC-10004 in Subjects with Active Psoriatic Arthritis"
NDA	New Drug Application
Papp 2012	Papp et al., "Efficacy of apremilast in the treatment of moderate to severe psoriasis: a randomised controlled trial," *Lancet*, 738-46 (2012)
PASI	Psoriasis Area and Severity Index
Pathan 2012	Pathan et al., "Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in ankylosing spondylitis," *Ann. Rheum. Dis.*, 0:1-6 (2012)
PBMC	Peripheral blood mononuclear cells
PDE	Phosphodiesterase enzyme
PDE IV or PDE4	Phosphodiesterase enzyme 4
PDX	Plaintiff's demonstratives
PTX	Plaintiff trial exhibit
POSA	Person of Ordinary Skill in the Art
Patent Office	U.S. Patent and Trademark Office
Sandoz	Sandoz Inc.

Term	Definition
Schett 2012	Schett et al., "Oral Apremilast in the Treatment of Active Psoriatic Arthritis," *Arthritis & Rheumatism*, 64(10): 3156-67 (2012)
SelCIDs	Selective cytokine inhibitory drugs
SOF	Stipulation of Facts
Suryanarayanan	Raj Suryanarayanan, *X-Ray Powder Diffractometry*, *in* Physical Characterization Of Pharmaceutical Solids (Harry G. Brittain ed., 1995)
Takeuchi	Takeuchi et al., "(R)- and (S)-3-Fluorothalidomides: Isosteric Analogues of Thalidomide," *Organic Letters*, 1(10), 1571-73 (1999)
TGA	Thermogravimetric analysis
TNFα or TNF-α	Tumor necrosis factor α
WO '606	WO 01/34606
WO '102	WO 2011/063102
Wu	Wu et al., "First-time-in-man, safety/tolerability and pharmacokinetics of ascending oral doses of apremilast (APR) in healthy subjects (HS), *Journal of Investigative Dermatology*, Vol. 131, No. 515 (2011)
XRPD	X-ray powder diffraction
Zydus	Zydus Pharmaceuticals (USA) Inc.

TABLE OF WITNESSES

Witness	Live or By Deposition	Description
Andrew Alexis, M.D., M.P.H.	Live	Dr. Alexis is Amgen's expert in the field of dermatology, including the treatment of dermatologic conditions such as psoriasis.
Stephen Davies, Ph.D., D.S.	Live	Dr. Davies is Amgen's expert in the field of synthetic, organic, and medicinal chemistry, including stereochemistry, and as well as in the synthesis and characterization of molecules and their use in pharmaceuticals.
Elaine S. Gilmore, MD, Ph.D.	Live	Dr. Gilmore is Defendants' expert in the field of dermatology, and specifically in the treatment of psoriasis.
Fabia Gozzo, Ph.D.	Live	Dr. Gozzo is Amgen's expert in the field of synchrotron radiation x-ray powder diffraction and structural characterization of materials.
Gordon W. Gribble, Ph.D.	Live	Dr. Gribble is Defendants' expert in the field of chemistry, organic chemistry, and medicinal chemistry, including stereochemistry and their use and development of pharmaceutical compositions.
Ivan T. Hofmann, C.P.A., C.F.F., C.L.P.	Live	Mr. Hoffmann is Defendants' expert in the field of pharmaceutical economics and market analysis, including economic issues involving intellectual property.
Susan Kim, Pharm.D.	By Deposition	Dr. Kim was Executive Director, U.S. Marketing at Amgen Inc. from November 2019 until her departure from Amgen in December 2020, and previously served in the same role at Celgene Corp. Dr. Kim was a Fed. R. Civ. P. 30(b)(6) corporate designee for Amgen.
Richard Knowles, Ph.D.	Live	Dr. Knowles is Amgen's expert in the field of biochemistry, pharmacology, and drug discovery, including in the field of PDE4 inhibitors.

Witness	Live or By Deposition	Description
Steven Miller, Ph.D.	Live	Dr. Miller is Zydus' expert in the field of characterization, identification and analysis of polymorphs.
George Muller, Ph.D.	By Deposition	Dr. Muller is a named inventor on the '536, '101, '283, and '638 patents.
Allan S. Myerson, Ph.D.	Live	Dr. Myerson is Amgen's expert in the field chemical engineering, the study of crystalline forms, and the pharmaceutical manufacturing, and industrial applications of crystallization in pharmaceutical formulations.
Clive Page, Ph.D.	Live	Dr. Page is Defendants' expert in the field of pharmacology and drug discovery, including in the field of PDE inhibitors and the treatment of inflammatory diseases.
Richard Person	By Deposition	Mr. Person is a Senior Commercial Counsel at Amgen and was a Fed. R. Civ. P. 30(b)(6) corporate designee for Amgen.
Patricia Rohane, Ph.D.	By Deposition	Dr. Rohane was Vice President, Clinical Research and Development, Immunology and Inflammation at Celgene Corp. from June 2003 until May 2010. Dr. Rohane is expected to testify about, among other things, Otezla®, its titration schedule, and its research and development, and clinical trials.
Mark J. Sacchetti, Ph.D.	Live	Dr. Sacchetti is Zydus' expert in the field of solid state chemistry, pharmaceutical science, polymorphism and polymorph screening.
Peter Schafer, Ph.D.	Live	Dr. Schafer is a named inventor on the '536, '101, '283, and '638 patents. Dr. Schafer was a Fed. R. Civ. P. 30(b)(6) corporate designee for Amgen.
Daniel O. Scharfstein, ScD	Live	Dr. Scharfstein is Defendants' expert in the field of biostatistics.

Witness	Live or By Deposition	Description
William Smith, Esq.	Live	Mr. Smith is Amgen's expert in Patent Office policies, practices, and procedures.
Johnathan W. Steed, Ph.D.	Live	Prof. Steed is Defendants' expert in the field of chemistry and crystallography.
Christopher Vellturo, Ph.D.	Live	Dr. Vellturo is Amgen's expert in the field of microeconomics, survey design and implementation, and the evaluation of commercial performance of pharmaceutical products.
Jean Xu	By Deposition	Ms. Xu is a named inventor on the '101 and '283 patents.

I. The Asserted Claims Of The '638 Patent Are Invalid.

A. Person Of Ordinary Skill In The Art For The '638 Patent.

1. A POSA with respect to the claimed subject matter would include a person who possesses an advanced degree (e.g., Master's degree or Ph.D., or foreign equivalents of either of the foregoing) in the fields of solid state chemistry or a related discipline, such as physical chemistry or pharmaceutical science, and several years of experience in the pertinent field. A POSA could have a lower level of formal education, such as a Bachelor's degree, if such a person had more years of experience in the field of pharmaceutical science or solid state chemistry. DFF ¶ 400; *Graham v. John Deere Co*., 383 U.S. 1, 148 USPQ 459 (1966).

2. A POSA would have worked as part of a team that included one or more other people of ordinary skill in the art with respect to one or more other aspects of the claims of the patents. The other people of ordinary skill in the art would have expertise and knowledge obtained through his or her educational, industrial, or academic experiences, including specialties in medicinal chemistry, organic or synthetic chemistry, pharmaceutical formulation, pharmacology, medicine, and clinical use. *Id*.

3. The Court finds Defendants' definition is the correct definition of a POSA as it stays true to the subject matter of the '638 patent. Amgen proposed an alternative definition of a POSA that does not afford enough education or experience to a POSA. DFF ¶ 401-403; *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 421 (2007).

B. The '638 Patent Priority Date Is March 20, 2002.

4. The earliest effective filing date for the '638 patent is March 20, 2002, the effective filing date of Provisional Application No. 60/366,515. DFF ¶ 404.

5. A patentee bears the burden to establish an earlier priority date by showing by a preponderance of evidence that the entire scope of the claimed subject matter was conceived and

reduced to practice at that earlier date. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1169 (Fed. Cir. 2006).

6. Conception occurs when the inventors possessed a definite and permanent idea of the entire scope of the claimed subject matter. *Burroughs Wellcome Co. v. Barr Laboratories, Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 2004) ("Thus, the test for conception is whether the inventor had an idea that was definite and permanent enough that one skilled in the art could understand the invention; the inventor must prove his conception by corroborating evidence, preferably by showing a contemporaneous disclosure. An idea is definite and permanent when the inventor has a specific, settled idea, a particular solution to the problem at hand, not just a general goal or research plan he hopes to pursue".); *see also Allergan, Inc. v. Apotex Inc.,* 754 F.3d 952, 967 (Fed. Cir. 2014) ("The invention date is the date of conception. Conception is the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.").

7. Reduction to practice is established by actual or constructive reduction to practice. Actual reduction to practice occurs when all of the following are satisfied: (1) construction of an embodiment meeting all elements of the claim, (2) determination that the invention would work for its intended purpose, and (3) the existence of evidence corroborating inventor testimony regarding these events. *Medichem*, 437 F.3d 1157, 1169 (Fed. Cir. 2006).

8. "In order to establish an actual reduction to practice, an inventor's testimony must be corroborated by independent evidence." *Cooper v. Goldfarb*, 154 F.3d 1321, 1330 (Fed. Cir. 1998).

9. Constructive reduction to practice occurs with the filing of the patent application. *Hyatt v. Boone*, 146 F.3d 1348 (Fed. Cir. 1998) (citing *Hybritech Inc. v. Monoclonal Antibodies, Inc*., 802 F.2d 1367, 1376 (Fed. Cir. 1986)).

10. The priority determination requires evidence showing that when the inventor first made the invention, "he understood his creation to have the features that comprise the inventive matter at bar." *Invitrogen Corp. v. Clontech Labs., Inc*., 429 F.3d 1052, 1064 (Fed. Cir. 2005). Thus, the proper analysis is focused on what the *inventor* recognized as of the alleged priority date not on a POSA's understanding.

11. The Court finds no evidence that the inventors of the '638 patent conceived of a "pharmaceutical composition comprising stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione" that is "suitable for oral administration" in amounts of "10 to 200 mg," as required by the asserted claims, by October 21, 1999. DFF ¶ 405-414; *Hitzeman v. Rutter*, 243 F.3d 1345, 58 USPQ2d 1161 (Fed. Cir. 2001).

12. Dr. Schafer provided no testimony for the Court as to when he had a definite and permanent idea of the complete and operative invention, did not testify that the thousands of compounds synthesized in Celgene's drug discovery program were suitable for oral pharmaceutical compositions, and did not testify that testing in a murine shock model assay was sufficient to show that apremilast would be useful for treating psoriasis. DFF ¶ 405-414; *Hybritech Inc. v. Monoclonal Antibodies, Inc*., 802 F.2d 1367, 1376 (Fed. Cir. 1986).

13. Dr. Schafer's testimony that Dr. Man isolated stereomerically pure apremilast in October 1999 and vague reference to Celgene's ongoing drug discovery program cannot legally establish conception and reduction to practice of oral pharmaceutical compositions comprising

stereomerically pure apremilast in dosage amounts ranging from 10 to 200 mg. DFF ¶ 405-414; *Medichem*, 437 F.3d at 1171-72 ("Even the most credible inventor testimony is *a fortiori* required to be corroborated by independent evidence, which may consist of documentary evidence or testimony of non-inventors.)

14. Amgen's evidence regarding apremilast's synthesis and testing in *in vivo* murine shock model, does not establish that the named inventors recognized that apremilast would be suitable for administering to a patient. Dr. Schafer, the only named inventor the Court heard from regarding this issue, testified that his team tested hundreds, if not thousands, of compounds synthesized in the chemistry group "to determine which compounds had the right pharmaceutical properties," that "[t]he murine shock model was the very first animal model that [they] would test the compounds in," and if a compound worked in this model, they would "go on to do further testing." DFF ¶¶ 413-14.

15. The Court finds that Amgen has not met its burden to establish priority before the March 20, 2002 filing date. Thus, the effective filing date of the '638 patent must be no earlier than March 20, 2002, the date of the earliest Provisional Application listed on the face of the '638 patent. DFF ¶ 404-414.

C. The '638 Patent Claims Are Anticipated By The '358 Patent.

16. A person is not entitled to a patent if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent," 35 U.S.C. § 102(a), or "the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States," 35 U.S.C. § 102(b).

17. A person is not entitled to a patent if "the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States

before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language." 35 U.S.C. § 102(e).

18. A patent is invalid if it is proven to be anticipated by clear and convincing evidence. *Microsoft Corp. v. i4i Partnership*, 564 U.S. 91, 95 (2011).

19. "The first step in any invalidity . . . analysis is claim construction." *See Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1362, 47 USPQ2d 1027, 1029 (Fed.Cir.1998). Claim construction is a question of law. *See Georgia–Pacific Corp. v. United States Gypsum Co*., 195 F.3d 1322, 1330, 52 USPQ2d 1590, 1597 (Fed. Cir. 1999). "In claim construction the words of the claims are construed independent of the accused product, in light of the specification, the prosecution history, and the prior art. . . . [T]he construction of claims is simply a way of elaborating the normally terse claim language[ ] in order to understand and explain, but not to change, the scope of the claims." *Scripps Clinic v. Genentech, Inc*., 927 F.2d 1565, 1580, 18 USPQ2d 1001, 1013 (Fed.Cir.1991) (internal quotation marks omitted); *see also Union Oil Co. of Cal. v. Atl. Richfield Co*., 208 F.3d 989, 994-95 (Fed. Cir. 2000).

20. Claims 3 and 6 of the '638 patent are directed to oral pharmaceutical compositions of stereomerically pure apremilast. Stereomerically pure means a composition that comprises one stereoisomer of a compound and is substantially free of other stereoisomers of that compound, and stereomerically pure apremilast means apremilast, the (+) isomer, substantially free of the (-) isomer. DFF ¶ 447.

21. The Court finds that the '358 patent discloses each element of claims 3 and 6 of the '638 patent: the '358 patent discloses stereomerically pure apremilast, oral pharmaceutical compositions with a pharmaceutically acceptable carrier, excipient, or diluent, with dosages overlapping in the range from 10 to 200 mg. A patent claim is anticipated (*i.e.*, not novel) if comparison of the claim with a prior art reference reveals that every element of the claim is described, either expressly or inherently, in the prior art reference. DFF ¶ 415-492; *Apotex*, 754 F.3d at 958 (citing *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)).

22. A POSA would understand the '358 patent to disclose, among other subject matter, pharmaceutical compositions suitable for oral administration comprising from about 10 mg to about 200 mg of stereomerically pure apremilast and a pharmaceutically acceptable carrier, excipient, or diluent. The '358 patent teaches every element of claims 3 and 6 of the '638 patent expressly and inherently. Thus, the Court finds claims 3 and 6 of the '638 patent are invalid for anticipation by the '358 patent. DFF ¶ 415-492; *Schering*, 339 F.3d at 1377.

23. Example 12 of the '358 patent explicitly discloses stereomerically pure apremilast: Example 12 of the '358 patent is a racemic mixture that is 50% of the (+) isomer, which is apremilast, and 50% the (-) isomer, the racemic mixture and the enantiomers have the same chemical formula and same atom-to-atom connections, and a POSA also understands claim 1 and Formula I of the '358 patent to cover apremilast. DFF ¶ 416-474; *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962).

24. The '358 patent explicitly discloses that "[t]he compounds of Formula I possess a center of chirality and can exist as optical isomers. Both the racemates of these isomers and the individual isomers themselves, as well as diastereomers when there are two chiral centers, are

within the scope of the present invention." The '358 patent also explicitly discloses mechanical and chemical separation techniques for compounds of Formula I. DFF ¶ 432-438, 471.

25. Either a single element of claimed subject matter or the entire claimed subject matter may be inherently disclosed. *Schering*, 339 F.3d at 1379. Inherency arises when a limitation not expressly found in a prior art reference is necessarily present based on what the prior art reference conveys to those of ordinary skill in the art. *See Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1368 (Fed. Cir. 2006). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999); *see also Schering*, 339 F.3d at 1377, 1379.

26. Example 12 of the '358 patent inherently discloses stereomerically pure apremilast. A reference includes an inherent characteristic if that characteristic is the "natural result" flowing from the reference's explicitly recited teachings. DFF ¶ 416-474; *see Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001). A compound (and therefore its inherent physical properties) may be deemed to have been inherently disclosed by a reference that teaches the manner by which that compound would have necessarily been made. *See Schering*, 339 F.3d at 1373, 1380; *see also Smithkline*, 403 F.3d at 1345 (finding inherent anticipation where production of PHC anhydrate in accordance with the prior art "inherently results in at least trace amounts of PHC hemihydrate."). Newly discovered results of known processes are inherent and unpatentable. *See Bristol-Meyers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001).

27. "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single

anticipating reference." *Schering*, 339 F.3d at 1377 (citing *Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)). "[I]nherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure." *Id*. (citing *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed. Cir. 2002)). This means evidence that was unavailable on the critical date can be used to support a defense of patent invalidity based on inherency. *Schering*, 339 F.3d at 1377. Disclosure of a definite and limited class of compounds is sufficient disclosure for anticipation of each member of the class that a person of ordinary skill in the art would envisage from reading the prior art reference. *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962).

28. Regardless of whether the '358 patent identifies apremilast by common name (i.e., apremilast) or by physical property (i.e., the (+) isomer of Example 12), a POSA would immediately understand Example 12 to disclose both the (+) and the (-) isomers of Example 12 and their chemical structures based on the entirety of Example 12. DFF ¶ 416-474. A POSA would also immediately understand Example 12 to a racemic mixture composed of each isomer in a 50:50 ratio. *Id*. With Example 12 in hand, a POSA would immediately envisage stereomerically pure apremilast based on the '358 patent's instructions to separate the isomers to greater than 95% optical purity using chiral chromatography. *Id.* A POSA following Example 12 and the instructions shown in columns 8 and 9 of the '358 patent regarding separation and purification of isomers using chiral chromatography would have necessarily obtained stereomerically pure apremilast having greater than 98% by weight of apremilast. *Id.* Thus, stereomerically pure apremilast is expressly and inherently disclosed by the '358 patent. *Allergan*, 754 F.3d at 958.

29. A POSA understands the '358 patent to disclose oral pharmaceutical compositions comprising stereomerically pure apremilast, with a pharmaceutically acceptable carrier, excipient, or diluent, wherein the amount of stereomerically pure apremilast is from 10 to 200 mg. DFF ¶ 475-482; *Telemac Cellular Corp. v. Topp Telecom, Inc*., 247 F.3d 1316, 1327-28 (Fed. Cir. 2001).

30. The Court finds that Amgen's argument that a POSA would not have recognized stereomerically pure apremilast in the '358 patent should be given no weight. DFF ¶ 204, 207, 212, 418-424; *Schering*, 339 F.3d at 1377 ("[I]nherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure.") (citing *In re Cruciferous Sprout Litig.*, 301 F.3d at 1351).

1. Enablement Of An Anticipatory Reference.

31. A prior art reference can be enabled for purposes of anticipation even if the disclosed embodiment was not actually made, and even if there is no evidence that the disclosed compound works for its intended purpose. *In re Gleave*, 560 F.3d 1331, 1334-36 (Fed. Cir. 2009) ("A thorough reading of our case law, however, makes clear that a reference need disclose no independent use or utility to anticipate a claim under § 102."); *Schering*, 339 F.3d at 1380; *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985). Indeed, the standard used to determine whether prior art provides an enabling disclosure under 35 U.S.C. § 102 is much less stringent than the test that must be employed with regard to 35 U.S.C. § 112. *See Gleave*, 560 F.3d at 1334-36 (Fed. Cir. 2009) (a prior-art reference may be enabling for the purposes of anticipation even if it would not "otherwise entitle its author to a patent" under the enablement requirement of 35 U.S.C. § 112).

32. Prior art references are presumed to be enabled. *See Proctor & Gamble Co. v. Nabisco Brands, Inc*., 711 F. Supp. 759, 772 (D. Del. 1989) (finding that P&G failed to meet its burden to show that the prior art was not enabling).

33. The Court finds Amgen failed to meet its burden of establishing that the '358 patent would not enable a POSA to obtain stereomerically pure apremilast. Amgen incorrectly applied only the *In re Wands* enablement test, arguing that the '358 patent needs to satisfy a heavier burden to be enabled as prior art than the Federal Circuit dictates. DFF ¶ 483-492. Under the correct legal standard, the '358 patent satisfies the necessary showing that a POSA would have the knowledge and skill to obtain stereomerically pure apremilast from Example 12 and other disclosures in the patent. *Gleave*, 560 F.3d at 1334-36. Thus, the '358 patent is enabled as a prior art reference to the '638 patent.

34. Even applying the *In re Wands* factors, the Federal Circuit has faced the issue of what disclosures are necessary to enable a claim to purified enantiomers and found disclosures even less specific than those in the '358 patent to be legally sufficient to establish enablement under § 112. "In view of the finding that enantiomer separation methods are well-known and routine to a person of ordinary skill, we agree with the district court that the inventors were not required to provide a detailed recipe for preparing every conceivable permutation of the compound they invented to be entitled to a claim covering that compound. Where a claim has been construed to cover a chemical compound, the specification is not deficient merely because it does not disclose how to prepare a particular form or mixture—among hundreds of possible permutations—of that compound." *Pfizer Inc. v. Teva Pharmaceuticals USA, Inc*., 555 Fed. App'x 961, 966-67 (2014).

35. Amgen's expert, Dr. Davies, testified at length about how difficult and unpredictable the practice of chiral allegedly is, but pointed to nothing about the racemic compound of Example 12 that would have led a POSA to believe that chiral chromatography would be insufficient to obtain apremilast. DFF ¶ 483-492. In light of this, the Court finds Dr. Davies' testimony has little weight.

36. The Court concludes separation of enantiomers using chiral chromatography is routine, standard experimentation taught in sophomore organic chemistry, and POSA would have been able to separate the (+) and (-) isomers of Example 12 of the '358 patent with routine experimentation.

37. The Court thus concludes '358 patent's "disclosure, coupled with the methods for synthesis and resolution that were found to be well-known and routine in the art, is sufficiently enabling." DFF ¶ 416-492; *Pfizer*, 555 Fed. App'x at 967 (2014).

D. The '638 Patent Claims Are Obvious.

38. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); *see also KSR*, 550 U.S. at 427 ("the results of ordinary innovation are not the subject of exclusive rights under the patent laws"). Where the patent is directed to a new treatment using a known compound, it is reasonable to assume that compounds with shared common properties are apt to share other related properties as well. *Anacor Pharms., Inc. v. Iancu*, 889 F.3d 1372, 1384 (Fed. Cir. 2018).

39. "Obviousness under 35 U.S.C. § 103(a) is ultimately a legal question, based on underlying factual determinations." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008). "The factual determinations underpinning the legal conclusion of obviousness

include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness." *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)); *see also Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259 (Fed. Cir. 2012).

40. A patent is invalid if it is proven to be obvious by clear and convincing evidence. *See, e.g.*, *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014); *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 993–94 (Fed. Cir. 2009).

41. Obviousness is judged as of the time the invention was made, from the viewpoint of a POSA. DFF ¶ 534-553; *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-20 (2007). Obviousness is demonstrated when "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble*, 566 F.3d at 994.

42. The fact that a reference was previously considered by the PTO does not increase the burden of proof or preclude a finding of invalidity but merely speaks to the weight of that reference's evidence. *See Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259-1260 (Fed. Cir. 2012) ("Whether a reference was previously considered by the PTO, the burden of proof is the same: clear and convincing evidence.") (citing *Microsoft Corp. v. i4i Ltd. P'ship*, 564 U.S. 91, 95 (2011)). A finding of invalidity may be appropriate where the reference was considered by the PTO, but the examiner failed to give proper consideration to the teachings of that reference. DFF ¶ 552-553; *see Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1366 (Fed. Cir. 2007).

43. Neither the combination of the '358 patent and WO '606 nor the combination of the '358 patent and Takeuchi were considered during the prosecution of the '638 patent. DFF ¶ 552-553; *Microsoft Corp.*, 564 U.S. at 109-112.

44. Obviousness is determined on a claim-by-claim basis, and the claim as a whole must be obvious. *KSR*, 550 U.S. at 406.

1. Scope And Content Of The Prior Art.

45. The scope of the prior art includes art that is "reasonably pertinent to the particular problem with which the inventor was involved." *In re GPAC Inc.*, 57 F.3d 1573, 1577 (Fed. Cir. 1995) (citation omitted). In determining whether the claimed invention falls within the scope of the relevant prior art, a court first examines, "the field of the inventor's endeavor" and "the particular problem with which the inventor was involved" at the time the invention was made. *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 411 F.3d 1332, 1339 (Fed. Cir. 2005). "A reference is reasonably pertinent if, even though it may be in a different field of endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *Id.* (citation omitted).

46. In determining obviousness, printed publications, patents, and patent applications all constitute prior art under 35 U.S.C. § 102. Specifically, art is prior art under § 102(a) if it was "patented" or "described in a printed publication . . . before the effective filing date of the claimed invention." 35 U.S.C. § 102(a); *see also Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996) ("under section 102(a), a document is prior art only when published before the invention date.").

47. A reference is prior art under § 102(b) if it was "patented or described in a printed publication . . . one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b).

48. A published patent application is prior art under § 102(e) if it was filed by another before the invention by the applicant for the patent. A patent granted on an application for patent by another filed in the United States before the invention by the applicant for the patent is also prior art under § 102(e).

49. Prior art references in an obviousness evaluation must be considered as a whole and are not limited to the particular invention they describe. *See, e.g.*, *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1076 (Fed. Cir. 2015) (*citing EWP Corp. v. Reliance Universal, Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985) ("A reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to protect."). This is true even if a particular embodiment of the invention is not the preferred embodiment. *See, e.g.*, *In re Arora*, 2010 WL 816569, at *2 (Fed. Cir. 2010) ("Dr. Arora argues that Andersson should be understood as limited to the narrow teaching that a smaller amount of a drug is needed when delivered via Andersson's inventive dry powder inhaler instead of a metered dose inhaler. It is well-settled, however, that a prior art reference must be considered for all that it teaches to those of ordinary skill in the art, not just the embodiments disclosed therein. Andersson teaches the broad principle that different drugs are equipotent at different dosages, and even provides an example of that principle."); *Purdue Pharma Prods., L.P. v. Par Pharm., Inc.*, Nos. 2009-1553, 2009-1592, 2010 WL 2203101, at *3 (Fed. Cir. 2010) ("[Prior art reference] renders the selection of tramadol obvious regardless of whether or not the patent lists tramadol as a preferred embodiment.").

50. While the cited prior art as a whole must enable a POSA to make and use the apparatus or method, each individual prior art reference is prior art, regardless of whether it alone provides an enabling disclosure. *See ABT Sys., LLC v. Emerson Elec. Co.*, 797 F.3d 1350,

1360 n.2 (Fed. Cir. 2015); *Geo M. Martin, Co. v. Alliance Mach. Sys. Int'l*, *LLC*, 618 F.3d 1294, 1302–03 (Fed. Cir. 2010); *Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1289, 1297 (Fed. Cir. 2010) (vacated for en banc rehearing on inequitable conduct).

51. Additionally, prior art references may be combined with the knowledge and/or experience of a POSA to "fill in the gap when limitations of the claimed invention are not specifically found in the prior art." *Belden Techs., Inc. v. Superior Essex Commc'ns LP*, 802 F. Supp. 2d 555, 563 (D. Del. 2011) (*citing Purdue Pharma Prods., L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 360 (D. Del. 2009); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013) ("[T]he knowledge of such an artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious.").

52. "What a reference teaches a [POSA] is not . . . limited to what a reference specifically 'talks about' or what is specifically 'mentioned or 'written' in the reference." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005).

53. Also, a determination that a claimed invention would be obvious, therefore "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418.

54. A POSA would have looked to and found the '358 patent when interested in finding new PDE IV inhibitors. DFF ¶ 493-504. A POSA would have looked to the 17 examples of the '358 patent, made those compounds, separated the enantiomers, and tested those for inhibition of PDE IV. A POSA would have arrived at apremilast because it is one of the enantiomers of those examples. *Id*; *Purdue Pharma Prods.*, 2010 WL 2203101, at *3 (Fed. Cir. 2010).

55. A POSA would have understood Example 12 of the '358 patent to disclose the racemic mixture comprising apremilast and its opposing enantiomer, and that the '358 patent teaches routine methods for separating such enantiomers by physical or mechanical means without the need for chemical modification. DFF ¶ 418-439, 493-504.

56. A POSA would have understood WO '606 to reinforce the teachings of the '358 patent, teach compounds of a Formula I that are useful for inhibiting PDE IV, and teach to preferably separate these compounds into the individual enantiomers such that each are substantially free of the other enantiomer. DFF ¶ 505-525.

57. A POSA would have understood Takeuchi to teach separation of the R- and S-enantiomers of 3-fluorothalidomide using a commercial chiral column, and that each enantiomer was obtained with an optical purity of more than 99% ee and each were tested for biological activity. DFF ¶ 528-532.

58. A POSA reading the '358 patent would have looked to Takeuchi because it teaches separation of enantiomers of a compound that has a phthalimid ring, just as disclosed in the '358 patent, and because Takeuchi teaches separation of the enantiomers to greater than 99% purity and subsequent biological testing of each enantiomer. DFF ¶ 533.

2. Differences Between The Claimed Invention And The Prior Art.

59. In determining the differences between the claimed invention and the prior art, obviousness is judged under "an expansive and flexible approach" driven by "common sense." *KSR*, 550 U.S. at 401, 403; *see also id.* at 421 (finding that the Federal Circuit "drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias," because "[r]igid preventative rules that deny factfinders recourse to common sense . . . are neither necessary under our case law nor consistent with it."); *Senju Pharm. Co. Ltd. v. Apotex Inc.*, 836

F. Supp. 2d 196, 208 (D. Del. 2011) ("The Supreme Court has emphasized the need for courts to value common sense over rigid preventative rules . . . .") (citation omitted).

60. In making this determination, the court must consider both the claimed invention and the prior art as a whole in light of the court's construction of the claims at issue. *See Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479-80 (Fed. Cir. 1998) ("In determining obviousness, the invention must be considered as a whole and the claims must be considered in their entirety").

61. "For obviousness, a single reference need not disclose every element of the claimed invention." *See, e.g.*, *Hospira, Inc. v. Amneal Pharm., LLC*, 285 F. Supp. 3d 776, 783 (D. Del. 2018) (citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

62. "While it may be easier to prove obviousness if each limitation of the claimed invention is found in the prior art, the level of skill of one of ordinary skill in the art can, at times, fill in the gap when limitations of the claimed invention are not specifically found in the prior art." *Belden Techs.*, 802 F. Supp. 2d at 563.

63. A conclusion of obviousness may be based on a single reference or a combination of prior art references. *See Senju Pharm.*, 836 F. Supp. 2d at 208 ("[A] defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed."); *see also In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("We see no clear error in the Board's determination as to the teachings of the prior art references, in combination.").

64. Where the issue of obviousness is based on a combination of elements, a claim is invalid for obviousness if "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention." *Pfizer*, 480 F.3d at 1361.

65. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416; *see also Q.I. Press Controls, B.V. v. Lee*, 752 F.3d 1371, 1379 (Fed. Cir. 2014) (same). This is because "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *KSR*, 550 U.S. at 402; *id.* at 427 ("We build and create by bringing to the tangible and palpable reality around us new works based on instinct, simple logic, ordinary inferences, extraordinary ideas, and sometimes even genius. These advances, once part of our shared knowledge, define a new threshold from which innovation starts once more. And as progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws.").

66. "Obviousness exists when 'a finite, and in the context of the art, small or easily traversed, number of options . . . would convince an ordinarily skilled artisan of obviousness.'" *Purdue Pharma*, 642 F. Supp. 2d at 368 (*quoting Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)); *see also C.W. Zumbiel Co., Inc. v. Kappos*, 702 F.3d 1371, 1387 (Fed. Cir. 2012) (finding obviousness where the invention involved "no more than the exercise of common sense in selecting one out of a finite—indeed very small—number of options"). In such a case, an invention is considered "obvious to try." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1332 (Fed. Cir. 2014) (finding claimed dosage obvious to try). Further, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill." *KSR*, 550 U.S. at 401. "When

the prior art provides the means of making the invention and predicts the results, and the patentee merely verifies the expectation through 'routine testing,' the claims are obvious." *Purdue*, 642 F. Supp. 2d at 368 (*citing Pfizer*, 480 F.3d at 1367).

67. "Obviousness does not require absolute predictability of success"; rather, "[a]ll that is required is a reasonable expectation of success" in making the invention via the combination. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation omitted); *see also Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 Fed. Appx. 289, 294 (Fed. Cir. 2011) ("[T]here is no requirement that a teaching in the prior art be scientifically tested or even guarantee success before providing a reason to combine. Rather, it is sufficient that one of ordinary skill in the art would perceive from the prior art a reasonable likelihood of success.") (citations omitted).

68. The Federal Circuit "has long rejected a requirement of '[c]onclusive proof of efficacy' for obviousness." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018) (and cases cited therein). Requiring testing for every possible configuration or combination in the prior art "improperly equates a reasonable expectation of success with absolute certainty." *See, e.g.*, *Hospira*, 285 F. Supp. 3d at 794 (citation omitted).

69. Prior to *KSR*, the Federal Circuit imposed a rigid "teaching-suggestion-motivation" test for obviousness. Under this test, the patent challenger was required to prove that "some motivation or suggestion to combine the prior art teachings" could be found "in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art." *KSR*, 550 U.S. at 407. The Supreme Court in *KSR* rejected the Federal Circuit's test in favor of a more flexible obviousness standard, stating that "the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take

account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

70. Under general obviousness analysis, the Court only must weigh whether the prior art would have led to the claimed subject matter using the flexible approaches set forth by the Supreme Court in *KSR*. *See Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) ("Requiring an explicit teaching to purify the 5(S) stereoisomer from a mixture in which it is an active ingredient is precisely the sort of rigid application of the TSM [teaching, suggestion, motivation] test that was criticized in *KSR*."). Moreover, as noted by the Supreme Court in *KSR* the standard for obviousness does not require absolute predictability of success, only a reasonable expectation given the knowledge and experience of a POSA. *KSR*, 550 U.S. at 420.

71. This more flexible standard expands the obviousness analysis beyond just "published articles and the explicit content of issued patents." *Id.* at 419. In broad terms, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420; *see also Perfect Web Tech., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1329 (Fed. Cir. 2009) ("We therefore hold that . . . an analysis of obviousness . . . may include recourse to logic, judgment, and common sense available to the person of ordinary skill that do not necessarily require explication in any reference or expert opinion.").

72. Courts have sought to determine whether "a person of ordinary skill, before the time of invention and without knowledge of that invention, would have found the invention merely an easily predictable and achievable variation or combination of the prior art." *Rolls-Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1338 (Fed. Cir. 2010). If so, then the invention likely

would have been obvious. *Id.* (citation omitted). "To preclude hindsight," the courts will take into account "evidence from before the time of the invention in the form of some teaching, suggestion, or even mere motivation . . . to make the variation or combination." *Id.* (citations omitted).

73. "[A] suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather 'may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.'" *Pfizer*, 480 F.3d at 1362 (Fed. Cir. 2007) (quoting *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).

74. "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *Id.* "[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute." *Life Techs., Inc. v. Clontech Lab., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000); *see also Std. Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("[O]ne should not go about determining obviousness under § 103 by inquiring into what patentees . . . would have known or would likely have done"). The inquiry into whether prior art teachings would have rendered the claimed invention obvious to one of ordinary skill in the art, is, as a matter of law, "independent of the motivations that led the inventors to the claimed invention." *Life Techs.*, 224 F.3d at 1325.

75. "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claim." *KSR*, 550 U.S. at 419-20; *see also Norgren Inc. v. ITC*, 699 F.3d 1317, 1324-26 (Fed. Cir. 2012) (affirming invalidity of claims under § 103 where

the claimed invention solved known problems by the use of an obvious solution). Even more, the discovery of a problem does not always result in a patentable invention. *Norgren*, 699 F.3d at 1327. For instance, an alleged invention is obvious in view of "evidence of known problems and an obvious solution." *Id.* Where a claim "simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 417 (quotation omitted).

76. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious. *KSR*, 550 U.S. at 421.

77. "When a work is available in one field, design incentives and other market forces can prompt variations of it, either in the same field or in another. If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability. Moreover, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill." *KSR*, 550 at 401.

78. None of "the length, expense, [or] difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably 'routine' to one of ordinary skill in the art." *Pfizer*, 480 F.3d at 1367. (DFF ¶ 493-553.)

79. A "claim to a product does not become nonobvious simply because the patent specification provides a more comprehensive explication of the known relationships between the variables and the affected properties." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1297 (Fed. Cir. 2012).

80. Even if a reference does not rise to the level of prior art, a court may consider it as motivation to combine. DFF ¶ 200-269; *see, e.g.*, *Lucent Techs., Inc. v. Gateway, Inc.*, 537 F. Supp. 2d 1095, 1102 (S.D. Cal. 2008) (*citing Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1337-38 (Fed. Cir. 2004)).

81. The motivation to combine inquiry is not limited to what products are forthcoming or currently available on the market, particularly given the lengthy FDA approval process. *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1324 (Fed. Cir. 2017); *see also id.* at 1326 ("'Motivation to combine may be found in many different places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications.'") (quoting *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013)). "Obviousness does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art does not teach away." *Id.* at 1328 (emphasis in original).

82. A *prima facie* case of obviousness exists where a claimed range and a prior art range are overlapping. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006). A *prima facie* case of obviousness further exists even where the claimed range and a prior range are not directly overlapping but are nevertheless close enough that one skilled in the art would have expected them to have the same properties. *See, e.g.*, *Titanium Metals Corp.*, 778 F.2d at 782-83 (affirming a rejection of a claim directed to an alloy "having 0.8% nickel, 0.3% molybdenum, up to 0.1% maximum iron, balance titanium" as obvious over a reference

disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31 molybdenum, balance titanium).

83. "To establish obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014); *see also Mead Johnson & Co. v. Premo Pharm. Labs*, No. 75-1230, 1980 U.S. Dist. LEXIS 15750, *103-04 (D.N.J. 1980). "Generally, an obviousness inquiry concerning such 'known compounds' focuses on the identity of a 'lead compound.'" *Bristol-Myers Squibb*, 752 F.3d at 973. "The motivation to modify that lead compound can come from any number of sources and need not necessarily be explicit in the art." *Id.*

84. The Federal Circuit's "lead compound test" applies only in one special situation, the determination of obviousness for a novel pharmaceutical compound, *i.e.*, a compound that was never previously disclosed in the prior art in any form. *See Novartis Pharm. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1059-60 (Fed. Cir. 2019).

85. The Federal Circuit's lead compound test examines whether a POSA would have had both: (1) a reason to select a lead compound—a compound with particular utility or properties of pharmacological interest—from the various compounds disclosed in the prior art; and (2) a motivation to make chemical modifications to that lead compound by adding or subtracting an atom or groups of atoms that would have resulted in the claimed compound. *See id*. at 1060 (finding that the District Court erred in applying the lead compound test to a method of treatment claim discussing a compound disclosed in the prior art).

86. The Federal Circuit has declined to extend this special test to the situation at bar, the separation of enantiomers from a disclosed racemate, because that encompasses a physical

separation of the disclosed components of the racemic mixture. *See Aventis Pharma*, 499 F.3d at 1301-03; *see also UCB, Inc. v. Accord Healthcare, Inc*., 890 F.3d 1313, 1328-29 (Fed. Cir. 2018) (declining to apply lead compound test to claim to enantiomers when racemate had been disclosed in the prior art). The separation of enantiomers from a racemic mixture requires does not chemically modify any compound because the chemical components of the enantiomers are not different when present in the racemic mixture or isolated in a more purified form. DFF ¶ 252, 279, 433, 435, 438, 450, 502, 515.

87. A "lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010). Rather, any known compound that has "promising useful properties" can be a lead compound that would have motivated "a chemist to make structurally similar compounds." *Id.*; *see also Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009) ("[T]o the extent Altana suggests that the prior art must point to only a single lead compound for further development efforts, that restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*.").

88. Conversely, the fact that many other compounds also could have been selected does not diminish the motivation to select a particular lead compound. *See id.* ("Altana suggests that the prior art would not have directed one of skill in the art to select compound 12 over the approximately 90 compounds claimed to be improvements in . . . prior art patents, or, for that matter, over the thousands of other compounds included in the prior art disclosures. . . . [T]he district court had a sufficient evidentiary basis for rejecting that position.").

89. In *UCB*, the district court found that a purified enantiomer was not obvious in light of the prior art disclosure of its racemate under a lead compound analysis focused on evaluation of pharmacological data and beneficial properties compared to other prior art compounds disclosed by the same inventors. *See UCB*, 890 F.3d at 1328-29. On appeal, the Federal Circuit affirmed the district court's holding but refused to require use of the lead compound test, noting that *Aventis* is the governing standard for claims to purified enantiomers, which only requires a motivation to purify the known mixture based on some desirable property. *Id*. at 1329. The *UCB* court found that even under *Aventis* "no clear error" existed in the district court's ultimate holding because there was no teaching in the prior art that the racemate had any beneficial properties or that the racemate could or should be separated into its enantiomers. *Id*. at 1328-29. Instead, the Federal Circuit noted the prior art taught that the racemate had inferior properties to other compounds identified by the inventors in their prior art patents and publications. *Id*.

90. An analysis selecting a lead chemical compound is not required to find obviousness, when the relevant chemical compound is known in the prior art. *See generally Pfizer*, 480 F.3d 1348 (finding obviousness of a claim directed to amlodipine besylate, where amlodipine was claimed in the prior art); *see also Novartis Pharm. Corp. v. West-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1060 (Fed. Cir. 2019) (where the patent-in-suit claimed a method of using the compound everolimus, the case did "not require lead compound analysis or analysis of whether a particular dose in a range of prior art doses would have been obvious", stating that "[t]o the extent the district court required a showing that a person of ordinary skill would have selected everolimus over other prior art compounds, it erred.").

91. The Federal Circuit has held that analyzing whether a prior art reference is enabling of the claimed subject matter has no place in an obviousness analysis. *See Raytheon Techs. Corp. v. Gen. Elec. Co.*, 993 F.3d 1374, 1380 (Fed. Cir. 2021) ("While a reference must enable someone to practice the invention in order to anticipate under § 102(b), a non-enabling reference may qualify as prior art for the purpose of determining obviousness under § 103.") (citing *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991)); *Beckman Instruments Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989) ("Even if a reference discloses an inoperative device, it is prior art for all that it teaches.").

92. The Court finds that the '358 patent discloses a limited and finite number of compounds that a POSA would understand are useful as lead compounds that could be tested in a routine manner to identify the most promising PDE4 and TNF-α inhibitors. DFF ¶ 504.

93. Independently, and optionally, "[o]bviousness based on structural similarity *may* be proven by identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound." *Altana*, 566 F.3d at 1007 (emphasis added); *accord Eisai*, 533 F.3d at 1357 ("obviousness based on structural similarity . . . *can* be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (*i.e.*, a lead compound) in a particular way to achieve the claimed compound") (emphasis added); *see also Ex Parte Cao*, 2011 WL 4434514, at *4 (B.P.A.I. Sept. 19, 2011) ("The *Eisai* court did not promulgate a per se rule that chemical compounds can only be held obvious if a lead compound is first identified.").

94. The inherency doctrine discussed with regard to anticipation may also apply to an obvious claim. *Allergan*, 726 F.3d at 1294 n.1.

3. Motivation.

95. The reason to combine prior art teachings need not be explicitly stated in any of the discussed references; it may come from any source including the POSA's knowledge and experience regarding the chemical similarity between two compounds. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361-62 (Fed. Cir. 2007); *see also SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000).

96. The Court concludes that a POSA would have been motivated with a reasonable expectation of success to separate the enantiomers of Example 12. DFF ¶ 534-547. Any time a POSA has a racemic mixture, the POSA is motivated to separate the isomers so that there is no longer a mixture of two things. *Id*.

97. A POSA would have been motivated with a reasonable expectation of success to test each enantiomer of Example 12, and any racemic mixture in any situation, in order to determine the relative biological activity of each. DFF ¶ 534-547. There is never not a motivation to separate racemic mixtures. *Id*.

98. The Court finds that WO '606 adds to a POSA's motivation to separate the enantiomers of Example 12 of the '358 patent because WO '606 teaches that compounds of Formula I preferably are administered as substantially chirally pure isomers. DFF ¶ 546.

99. The Court finds Takeuchi adds to a POSA's motivation to separate the enantiomers of Example 12 because Takeuchi was able to separate the enantiomers of 3-fluorothalidomide to 99% optical purity, and these compounds are related to apremilast via the phthalimid ring structure, and Takeuchi teaches to test each enantiomer for biological activity and finds that one enantiomer is more active than the other. DFF ¶ 547.

4. Reasonable Expectation Of Success.

100. The Court finds an enantiomer present in a pharmaceutically active racemic mixture is *prima facie* obvious over the prior art disclosure of the racemate "even without an explicit teaching that the ingredient [*i.e.*, enantiomer] should be concentrated or purified." DFF ¶ 548-558; *Aventis Pharma*, 499 F.3d at 1301-02; *see also In re Adamson*, 275 F.2d 952, 954–55 (C.C.P.A. 1960) (holding that an isolated stereoisomer is obvious over the prior art disclosure of the racemate given insufficient showing of any unexpected result, explaining that following the prior art teachings is doing "no more than the obvious" where the prior art suggests to a POSA that the racemates disclosed in a reference may be resolved into their individual enantiomers).

101. Under the *Aventis* standard, Dr. Gribble offered clear and convincing evidence that claims 3 and 6 of the '638 patent would have been obvious based on the teachings of the '358 patent when combined with the teachings of either (1) Celgene's WO '606 or (2) Takeuchi, in addition to the knowledge of a POSA. DFF ¶ 493-558.

102. The Court concludes POSA would have been motivated by the combined teachings of the '358 patent and WO '606 to separate the enantiomers of Example 12 and would have reasonably expected to obtain optical purity greater than 98%. DFF ¶ 550-552. Possessing the pure enantiomers, the POSA would have been motivated by the combined teachings of the '358 patent and WO '606 to test both enantiomers for PDE4 inhibition and then reasonably would have expected that one or both of these enantiomers would inhibit PDE4. *Id*.

103. A POSA with the optically pure enantiomers of Example 12 would have been motivated by the combined teachings of the '358 patent and WO '606 to formulate apremilast into an oral pharmaceutical composition containing anywhere from 10 to 200 mg of the stereomerically pure enantiomers with a reasonable expectation of success. DFF ¶ 550-552.

104. The Court concludes that the combined disclosures of the '358 patent and WO '606 teach all elements of claims 3 and 6 of the '638 patent. DFF ¶ 527.

105. In light of the combined teachings of the '358 patent and Takeuchi, a POSA would have been motivated to apply the teachings of Takeuchi to Example 12 of the '358 patent and would have reasonably expected to obtain stereomerically pure apremilast with optical purity of 99% or greater. DFF ¶ 533, 547, 553.

106. A POSA would have been motivated with a reasonable expectation of success to arrive at the subject matter of claims 3 and 6 of the '638 patent based on the combined teachings of the '358 patent and Takeuchi, which teach to separate enantiomers to 99% stereomeric purity and test and formulate the enantiomers into oral dosage forms in the range of 10 to 200 mg. DFF ¶ 533, 547, 553.

107. The Court concludes that the combined disclosures of the '358 patent and Takeuchi teach all elements of claims 3 and 6 of the '638 patent. DFF ¶ 533, 547, 553.

108. The '638 patent states that the enantiomers of Example 12 can be separated using known techniques. DFF ¶ 554-557. Statements to a patent office made during prosecution of a patent application and concerning the scope of prior art are binding admissions in subsequent litigation. *See Procter & Gamble Co. v. Nabisco Brands, Inc.*, 711 F. Supp. 759, 770 (D. Del. Apr. 4, 1989) ("a patentee's representations to the PTO during the prosecution of its patent application about the scope of the prior art is a binding admission and should 'be accepted at face value' during subsequent litigation over the patent.").

109. The '638 patent states that the racemate "is readily prepared using the methods in U.S. Patent No. 6,020,358, which is incorporated herein by reference. The '638 patent further states that compound A [apremilast] can be isolated from the racemic compound by techniques

known in the art. Examples include, but are not limited to, the formation of chiral salts and the use of chiral or high performance liquid chromatography "HPLC" and the formation and crystallization of chiral salts." DFF ¶ 554-557.

110. The '638 patent lists three different references that describe general methods that a POSA could use to resolve a compound. DFF ¶ 554-557. The inventors of the '638 patent signed an oath affirming the statements in the file history. *Id*. Statements and actions of the assigning patentee before a patent office are binding admissions upon the assignee. *Sherwin-Williams Co. v. PPG Indus., Inc*., 2021 WL 211497, at *2-3 & n.3 (W.D. Pa. Jan. 21, 2021) (Sherwin-Williams bound by the "Valspar admissions" during prosecution where it was "undisputed that Sherwin [was] Valspar's successor-in-interest."). A patent owner cannot avoid the consequences of the previous owner's statements simply because they were not an owner at the time the statements were made. *Eastman Kodak Co. v. Goodyear Tire, & Rubber Co*., 114 F.3d 1547, 1559 (Fed. Cir. 1997) ("Zimmer's actions prior to the assignment of the patent rights are imputed to Eastman. A patentee cannot avoid the consequences of his laches by transferring the patent.")

111. By acquiring apremilast, the Otezla® drug product, and the '638 patent, Amgen adopted Celgene's statements regarding the content and scope of prior art to the '638 patent, which includes statements regarding the content and scope of the '358 patent. *See Pfizer Inc. v. Teva Pharms. USA, Inc*., 2006 WL 3041102, at *5 (D.N.J. Oct. 26, 2006) ("Pfizer cannot use the expert affidavits to support its European patent application and then deny that its accepts the truth of the information contained therein."). DFF ¶ 554-557.

E. Claim 31 Of The '243 Patent Render The '638 Patent Claims Obvious.

112. "While often described as a court-created doctrine, obviousness-type double patenting is grounded in the text of the Patent Act." *Abbvie Inc. v. Kennedy Institute of*

Rheumatology Trust, 764 F.3d 1366,1372 (Fed. Cir. 2014). Under the obvious-type double-patenting invalidity doctrine, the law prevents a patentee from extending the term of exclusivity for a single invention by obtaining additional patents with only obvious variations from the earlier-expiring invention. *See, e.g., Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc.*, 98 F.3d 1563, 1568 (Fed. Cir. 1996); *Sun Pharma. Indus., Ltd. v. Eli Lilly and Co.*, 611 F.3d 1381, 1387 (Fed. Cir. 2010) (affirming summary judgment that claims to a method of using a certain compound as a cancer treatment were invalid for obviousness double-patenting based on a second patent, with the same filing date, claiming the compound and methods of using the compound for treating viral infections); *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1372-1273 (Fed. Cir. 2005).

113. Celgene's patent prosecution strategy has resulted in an unlawful extension of Amgen's monopoly and runs afoul of the axiom that a patentee may not claim the same invention in different patents with different expiration dates. DFF ¶ 559-562; *see Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1212 (Fed. Cir. 2014) ("[i]t is self-evident that on the expiration of a patent the monopoly created by it ceases to exist, and the right to make the thing formerly covered by the patent becomes public property. It is upon this condition that the patent is granted.") (quoting *Singer Mfg. Co. v. June Mfg. Co.*, 163 U.S. 169, 185 (1896).)

114. Obviousness-type double patenting is a question of law. *See, e.g., Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008).

115. The obviousness-type double patenting analysis entails two steps: (1) construction of the claim(s) in the earlier patent and the claim in the later patent to identify any differences; and

(2) making a determination of whether the differences in subject matter between the claims render the claims patentably distinct. *See, e.g., Eli Lilly*, 251 F.3d at 968.

116. The disclosures of the earlier-expiring patent may be used to determine the meaning of terms in a claim and may also be used as required to answer the second step above. *In re Vogel*, 422 F.2d 438, 441–42 (C.C.P.A. 1970); *In re Hitachi Metals, Ltd.*, 2015 WL 1187360, at *3-*4 (Fed. Cir. 2015). Typically, the specification sets forth at least one tangible embodiment within the claim, and it is less difficult and more meaningful to judge whether that thing has been modified in an obvious manner. "[I]t is also well settled that [a court] may look to a reference patent's disclosures of utility to determine the question of obviousness." *Abbvie*, 764 F.3d at 1380-81; *see also Sun*, 611 F.3d at 1387-88 (internal citations omitted).

117. The second step of the analysis is similar to an obviousness analysis under §103 in that the court must determine whether a POSA would consider the later invention an obvious variation of the prior invention. *See, e.g., Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1297-98 (Fed. Cir. 2012). However, there are some differences between the double-patenting analysis and the obviousness analysis. For example, obviousness under §103 compares claimed subject matter to the prior art as a whole, while non-statutory double patenting compares claims in an earlier patent to claims in a later patent or application. *See, e.g., id*. Also, "[t]he patent principally underlying the double patenting rejection need not be prior art." *Id.*

118. Claims 3 and 6 of the '638 patent are not patentably distinct from claim 31 of the '283 patent because the difference between the asserted claims and the reference claim would have been obvious to a person of ordinary skill in the art in light of the prior art. DFF ¶ 559-562; *see, e.g., Amgen Inc. v. F. Hoffman-La Roche, Ltd.*, 580 F.3d 1340, 1361 (Fed. Cir. 2009).

119. The ’638 and ’283 patents were both assigned by the named inventors to Celgene, which subsequently assigned both patents to Amgen. DFF ¶ 559. Obviousness-type double patenting extends to commonly owned patents with different inventive entities. *See, e.g., In re Hubbell*, 709 F.3d 1140, 1146-48 (Fed. Cir. 2013); *In re Longi*, 759 F.2d 887, 893–94 (Fed. Cir. 1985).

120. Claims 3 and 6 of the ’638 patent recite a broad genus of oral pharmaceutical compositions comprising stereomerically pure apremilast without limitation to the solid form of that apremilast. DFF ¶ 559-562. Claim 31 of the ’283 patent includes every limitation of claims 3 and 6 of the ’638 patent and merely limits the solid form to a particular polymorph of stereomerically pure apremilast. *Id*. It is well settled that a later-expiring patent claim covering a broader genus is invalid for obviousness-type double patenting based on an earlier-expiring reference claim covering a species within that genus. *Eli Lilly Co. v. Barr Laboratories Inc*., 251 F.3d 955, 970 (Fed. Cir. 2001).

121. Patent term extensions under the Hatch–Waxman Act may be challenged only under some circumstances, such as gamesmanship on the part of the patentee. *Novartis AG v. Ezra Ventures LLC*, 909 F.3d 1367, 1375 (Fed. Cir. 2018). (DFF ¶ 559-562.)

122. Patent term adjustments resulting from delays of the Patent Office are not shielded from challenge under obviousness-type double patenting because patentees have the right to invoke terminal disclaimers that render double patenting defenses moot. *Abbvie*, 764 F.3d at 1373. Thus, the ’638 is not entitled to its 609 day patent term adjustment because it is invalid for obviousness-type double patenting over claim 31 of the ’283 patent. DFF ¶ 559-562.

II. The Asserted Claims Of The ‘536 Patent Are Invalid.

A. The Person Of Ordinary Skill In The Art For The ’536 Patent.

123. The Court finds a POSA for the '536 patent is a scientist with a Ph.D. in a field such as pharmacology, with one or two years of experience in research and development of pharmaceutical compounds, or would have had a Master's or similar degree, as well as three or more years of experience in research and development of pharmaceutical compounds. DFF ¶ 702. "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR*, 550 U.S. 398, 421 (2007).

124. Further, the Court finds the POSA would be part of a team involved in the discovery and development of a new drug and typically include medicinal chemists, pharmacologists, toxicologists, formulation and scale up scientists, regulatory affairs specialists, clinicians with relevant experience in the treatment of therapeutic areas under consideration, and persons with commercial/marketing expertise. DFF ¶ 703.

B. The '536 Patent Priority Date Is March 20, 2002.

125. Parties agree that the '536 patent's priority date is March 20, 2002, which is the effective filing date of Provisional Application No. 60/366,515. DFF ¶ 707. A patentee bears the burden to establish an earlier priority date by showing by a preponderance of evidence that the entire scope of the claimed subject matter was conceived and reduced to practice at that earlier date. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1169 (Fed. Cir. 2006).

C. Technical Background.

1. Apremilast.

126. The Court concludes apremilast was specifically disclosed in the '358 patent in its racemic form as one of the compounds of "Formula I," which are disclosed as selective PDE4 inhibitors that decrease the levels of TNF-α and are therapeutically useful for treating immune and inflammatory conditions. DFF ¶ 709. *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1570 (Fed. Cir 1988). As discussed above with respect to the '638 patent, the lead

compound test does not apply with respect to a compound that has already been disclosed in the prior art, and particularly to claims associated with a purified enantiomer, when a racemic mixture containing that enantiomer was taught in the prior art. Thus, the Court gives no weight to Dr. Knowles' lengthy testimony on why a pharmacologist would or would not select apremilast as a lead compound.

2. Psoriasis.

127. Measurement of the levels of TNF-α produced by peripheral blood monocytes (PBMC) obtained from psoriasis patients showed that TNF-α produced by these cells is significantly higher compared to the levels produced by PBMC obtained from healthy subjects. Mizutani states that the results strongly suggest that inflammatory cytokines, especially TNF-alpha, from monocytes are involved in the pathogenesis of psoriasis. This provided a POSA with motivation to reduce levels of TNF-α in a person with psoriasis to contribute to an anti-inflammatory effect. DFF ¶ 717.

a. Treatment Of Psoriasis.

128. A POSA would have understood that, prior to 2002, there were a number of conventional topical and systemic therapies available for the treatment of psoriasis. DFF ¶¶ 718-727. Each of these therapies had its own advantages and disadvantages. This would have motivated a POSA to continue looking for new psoriasis therapies. *KSR*, 550 U.S. at 420.

3. PDE4 Inhibitors.

129. There are multiple families of phosphodiesterases ("PDEs"), enzymes that regulate the levels of the intracellular signaling molecule cyclic adenosine monophosphate (c-AMP). PDE enzymes are responsible for the inactivation of cAMP. It has long been appreciated that non-selective inhibitors of PDEs (such as theophylline) could have clinical benefit in a number of diseases. However, it was also recognized that by inhibiting these PDEs non-

selectively, there were also a number of unwanted side effects as these PDEs were found in many cell types beyond those targeted to obtain clinical benefit. The recognition by the end of the 1980s that there was cellular and tissue selectivity of where particular PDEs were located provided the logic and the motivation to find drugs that were selective inhibitors for particular PDEs that could have clinical benefit. DFF ¶¶ 728-729.

a. Inhibiting the PDE4 Enzyme to Reduce TNFα Production

130. When an inflammatory cell is exposed to a PDE4 inhibitor, PDE4 is inhibited, which causes levels of c-AMP to rise, which results in greater inhibition of the release of TNF-α from that cell. DFF ¶ 737.

b. PDE4 Inhibitors in the Treatment of Inflammatory Conditions, Including Psoriasis

131. The Court concludes there were are many observations in the literature reporting that selective PDE4 inhibitors have broad anti-inflammatory activity that is recognized in various reviews. It has also long been recognized that selective PDE4 inhibitors can suppress the release of a range of inflammatory mediators from inflammatory cells. These effects provided a strong scientific rationale for the development of selective, orally active, PDE4 inhibitors as novel treatments for a wide range of inflammatory diseases. DFF ¶ 741.

D. Scope And Content Of The Prior Art.

132. The scope of the prior art includes art that is "reasonably pertinent to the particular problem with which the inventor was involved." *In re GPAC Inc.*, 57 F.3d at 1577 (citation omitted). In determining whether the claimed invention falls within the scope of the relevant prior art, a court first examines, "the field of the inventor's endeavor" and "the particular problem with which the inventor was involved" at the time the invention was made. *Princeton Biochemicals, Inc.*, 411 F.3d at 1339. "A reference is reasonably pertinent if, even

though it may be in a different field of endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *Id.* (citation omitted).

133. In determining obviousness, printed publications, patents, and patent applications all constitute prior art under 35 U.S.C. § 102. Specifically, art is prior art under § 102(a) if it was "patented" or "described in a printed publication . . . before the invention thereof by the applicant for patent." 35 U.S.C. § 102(a); *see also Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996) ("under section 102(a), a document is prior art only when published before the invention date.").

134. A reference is prior art under § 102(b) if it was "patented or described in a printed publication . . . one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b).

135. Prior art references in an obviousness evaluation must be considered as a whole and are not limited to the particular invention they describe. *See, e.g.*, *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1076 (Fed. Cir. 2015) (*citing EWP Corp. v. Reliance Universal, Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985) ("A reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to protect."). This is true even if a particular embodiment of the invention is not the preferred embodiment. *See, e.g.*, *In re Arora*, 2010 WL 816569, at *2 ("Dr. Arora argues that Andersson should be understood as limited to the narrow teaching that a smaller amount of a drug is needed when delivered via Andersson's inventive dry powder inhaler instead of a metered dose inhaler. It is well-settled, however, that a prior art reference must be considered for all that it teaches to those of ordinary skill in the art, not just the embodiments disclosed therein. Andersson teaches

the broad principle that different drugs are equipotent at different dosages, and even provides an example of that principle."); *Purdue Pharma Prods., L.P. v. Par Pharm., Inc.*, Nos. 2009-1553, 2009-1592, 2010 WL 2203101, at *3 (Fed. Cir. 2010) ("[Prior art reference] renders the selection of tramadol obvious regardless of whether or not the patent lists tramadol as a preferred embodiment.").

136. While the cited prior art as a whole must enable a POSA to make and use the apparatus or method, each individual prior art reference is prior art, regardless of whether it alone provides an enabling disclosure. *See ABT Sys.*, 797 F.3d at 1360 n.2; *Geo M. Martin, Co. v. Alliance Mach. Sys. Int'l, LLC*, 618 F.3d 1294, 1302–03 (Fed. Cir. 2010); *Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1289, 1297 (Fed. Cir. 2010) (vacated for en banc rehearing on inequitable conduct).

137. Additionally, prior art references may be combined with the knowledge and/or experience of a POSA to "fill in the gap when limitations of the claimed invention are not specifically found in the prior art." *Belden Techs., Inc. v. Superior Essex Commc'ns LP*, 802 F. Supp. 2d 555, 563 (D. Del. 2011) (*citing Purdue Pharma Prods., L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 360 (D. Del. 2009); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013) ("[T]he knowledge of such an artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious.").

138. "What a reference teaches a [POSA] is not . . . limited to what a reference specifically 'talks about' or what is specifically 'mentioned or 'written' in the reference." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005).

1. The '358 Patent.

139. The Court finds Dr. Knowles' opinions that a POSA would not have believed the teachings of the '358 patent that all of the compounds disclosed therein were inhibitors of TNF-α

(DFF ¶ 766) are legally insufficient to rebut anticipation. Dr. Knowles misconstrued the facts and the law when he implied the prior art taught away from pursuing compounds such as apremilast. "A reference teaches away when it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought" by the patentee. *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (quotations omitted). Amgen's experts, including Dr. Knowles, pointed to no reference disparaging apremilast or offering reasons why it would not be an effective treatment for psoriasis. *See Galderma* 737 F.3d at 738 ("A reference does not teach away…if it expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed."). *See Gleave*, 560 F.3d at 1334-36 ("A thorough reading of our case law, however, makes clear that a reference need disclose no independent use or utility to anticipate a claim under § 102.").

140. The Court concludes that a POSA reading the '358 patent would understand that it describes molecules that are PDE4 inhibitors that can reduce undesirable levels of TNF-α. DFF ¶ 767. The '358 patent discloses compounds that are used for inhibiting PDE4 and inhibiting TNF-α and in treating diseases that are mediated by PDE4, such as psoriasis. DFF ¶ 768. A POSA reading the '358 patent would recognize a method of treating psoriasis with the disclosed compounds, including administering to a patient having psoriasis stereomerically pure apremilast. DFF ¶ 769.

2. Dyke 1999.

141. Dyke et al., "The Therapeutic Potential of PDE4 Inhibitors," *Expert Opinion on Investigational Drugs*, 8(9): 1301–1325 (1999) ("Dyke 1999") is an article that was published in 1999 (SOF ¶ 129) and is prior art to the '536 patent under § 102(b). DFF ¶ 770.

142. A POSA would understand that Dyke 1999 teaches that a number of groups have investigated the effect of PDE4 inhibitors on skin. It was shown that treatment of epidermal basal cells, in primary culture, with the PDE4 inhibitor Ro20-1724, leads to a threefold increase in cAMP concentrations, illustrating that these cells contain active PDE4 protein. A similar study comparing the effects of Ro20-1724 on psoriatic epidermal slices and keratomed psoriatic epidermal slices showed a very marked elevation of cAMP over controls (1395% increase in cAMP in keratomed psoriatic epidermis), suggesting that PDE4 inhibitors may be potentially beneficial in psoriasis. As for the inflammatory component of the disease, PDE4 inhibitors have been shown to inhibit the inflammatory response of a number of mediators *via* either topical or systemic administration. DFF ¶ 784.

143. In the clinic, topical administration of the selective PDE4 inhibitor, Ro20-1724, was investigated in two double-blind studies comparing its effectiveness to vehicle. These studies showed that PDE4 inhibition improve[d] psoriatic lesions and had no adverse systemic or cutaneous effects, suggesting the therapeutic potential of such compounds in the treatment of psoriasis. DFF ¶ 785.

3. Marriott 2001.

144. Marriott et al., "Immunotherapeutic and antitumor potential of thalidomide analogues," *Expert Opin. Biol. Ther*., 1(4): 675–682 (2001) ("Marriott 2001") is an article that was published in 2001 (SOF ¶ 131) and is prior art under to the '536 patent under at least 35 U.S.C. § 102(a). DFF ¶¶ 786-787.

145. Marriott 2001 generally discloses the immunotherapeutic and antitumor potential of thalidomide analogues and discloses that thalidomide was established as an effective immunomodulatory and anti-inflammatory drug which showed potential in treating a range of conditions, including rheumatoid arthritis. Celgene initiated a medicinal chemistry program to

design and prepare thalidomide analogs, and the initial focus of that program was to improve thalidomide's anti-TNF-α properties. DFF ¶ 788.

146. The design of compounds based on the thalidomide structure has led to the synthesis of analogues with greatly enhanced immunological activity and with similarly decreased toxicity. These analogues fall into at least two categories, one of which is selective cytokine inhibitory drugs (SelCID) which are phosphodiesterase Type 4 (PDE4 inhibitors). DFF ¶ 793.

147. In preclinical studies, the SelCID analogues were shown to be potent PDE4 inhibitors and this activity appear[ed] to correlate well with TNF-α inhibition. Marriott 2001 further discloses that clinical development of the SelCID compounds have been underway for the past five years although no clinical data has yet been published. DFF ¶ 794.

148. The first SelCID to enter into clinical development was CDC-801, which is approximately 10-fold more potent a TNF-α inhibitor than thalidomide and was found to be non-teratogenic. Marriott 2001 provides that CDC-801 successfully completed two Phase I clinical trials in the UK, with no serious adverse events reported. For CDC-801 to get into clinical trials, it would have had to pass through all the necessary preclinical and regulatory safety experiments. This would include toxicity studies that occurred over a chronic period of treatment, which would help determine the dose that would be allowed to be used in man for the first time, in human clinical trials. In 2001, CDC-801 was also being evaluated in a phase II clinical trial. Phase I and Phase II studies are conducted in humans. DFF ¶ 795.

149. A second SelCID that had begun clinical development was CDC-998, which was approximately 1000-fold more potent than thalidomide in inhibiting TNF-α in LPS stimulated human PBMC. Marriott 2001 reports that CDC-998 has completed initial preclinical safety

studies and has now moved forward into a Phase I trial programme that was initiated in the UK at the end of 2000. CDC-998 was also studied in a dog model and no emetic effects were shown. DFF ¶ 796.

150. As such, Marriott 2001 concludes that laboratory studies and initial clinical studies are encouraging and that the novel compounds therein may provide a new generation of clinically effective drugs. DFF ¶ 797.

4. Muller 1998.

151. Muller et al., "Thalidomide Analogs and PDE4 Inhibition," *Bioorganic & Medicinal Chemistry Letters*, 8: 2669–2674 (1998) ("Muller 1998") is an article that was published in 1998 (SOF ¶ 133), and is prior art to the '536 patent under 35 U.S.C. § 102(b). DFF ¶ 798.

152. Muller 1998 describes the efforts of Celgene to prepare several analogues of thalidomide and evaluate their ability to inhibit TNF-α and PDE4 *in vitro*, as well as decreasing the teratogenic potency of the thalidomide analogues. DFF ¶ 800.

153. Muller 1998 generally discusses thalidomide analogs and their ability to inhibit PDE4, and therefore an ability to inhibit TNF-α. Muller 1998 states that excessive TNF-α levels have been found to be associated with a number of inflammatory and autoimmune conditions including rheumatoid arthritis. Muller 1998 also teaches that control of TNF-α levels could be a key to the treatment of a wide range of disease and that the validity of this approach has recently been demonstrated by the clinical benefit observed in the treatment of rheumatoid arthritis and Crohn's disease by TNF-α antibodies and TNF-α soluble receptors. DFF ¶ 801.

154. Muller 1998 also discloses that in a program to increase the TNF-α inhibitory potency of thalidomide and eliminate/decrease its teratogenic potency, the authors prepared numerous analogs of thalidomide. Muller 1998 also states that these thalidomide analogs are

potent inhibitors of PDE4 and that it is proposed that these thalidomide analogs control TNF-α levels by inhibition of PDE4. DFF ¶ 802.

155. Based on the results, Muller 1998 stated that these thalidomide analogues are potent inhibitors of PDE4 and are able to control TNF-α levels by inhibition of PDE4. DFF ¶ 806.

E. The Asserted Claim Of The '536 Patent Is Invalid As Anticipated By The '358 Patent.

156. A person is not entitled to a patent if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent," 35 U.S.C. § 102(a), or "the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States," 35 U.S.C. § 102(b).

157. A person is not entitled to a patent if "the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language." 35 U.S.C. § 102(e).

158. A patent is invalid if it is proven to be anticipated by clear and convincing evidence. *Microsoft*, 564 U.S. at 95.

159. "The first step in any invalidity ... analysis is claim construction." *See Rockwell*, 147 F.3d at 1362. Claim construction is a question of law, which this court reviews without

deference. *See Georgia–Pacific*, 195 F.3d at 1330. "In claim construction the words of the claims are construed independent of the accused product, in light of the specification, the prosecution history, and the prior art.... [T]he construction of claims is simply a way of elaborating the normally terse claim language[ ] in order to understand and explain, but not to change, the scope of the claims." *Scripps*, 927 F.2d at 1580 (internal quotation marks omitted). *Union Oil*, 208 F.3d at 994-95.

1. The '358 Patent Discloses Stereomerically Pure (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione That Comprises Greater Than About 97% by Weight of (+) Isomer.

160. As set forth above, the Court finds that the '358 patent explicitly and inherently anticipates "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," and "a pharmaceutically acceptable salt thereof," as recited in the asserted claims of the '638 patent. DFF ¶ 809. A patent claim is anticipated (*i.e.*, not novel) if comparison of the claim with a prior art reference reveals that every element of the claim is described, either expressly or inherently, in the prior art reference. *Apotex*, 754 F.3d at 958 (citing *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)).

161. For all the same reasons set forth above, the Court concludes that the '358 patent also explicitly and inherently anticipates "stereomerically pure compound comprises greater than about 97% by weight of (+) isomer," as recited in claim 6 of the '536 patent. DFF ¶ 810. *Schering*, 339 F.3d at 1377.

2. Celgene's Admissions Regarding The Disclosure Of The '358 Patent.

162. The Court finds that Celgene's statements regarding the disclosure of optical purity in the counterpart to the '358 patent support that the '358 patent discloses the

"stereomerically pure compound comprises greater than about 97% by weight of (+) isomer," as recited in claim 6 of the '536 patent for the same reasons set forth above. DFF ¶ 811.

3. The '358 Patent Discloses The Method Of Treatment Limitations In Claim 6 Of The '536 Patent.

163. The '358 patent discloses certain compounds, their use in inhibiting phosphodiesterases, particularly PDE4, and in the treatment of diseases mediated by inhibition of PDE4. DFF ¶ 812.

164. Based on the disclosures in the '358 patent, a POSA would have understood that an oral dosage form containing from 1 to 100 mg of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione would be therapeutically effective for treating psoriasis. In addition, the dosage range in the '358 patent (1-100 mg) overlaps considerably with the dosage range in claim 6 of the '536 patent (10-200 mg). DFF ¶ 815. *Galderma*, 737 F.3d at 738.

165. The '358 patent also specifically discloses administration in single or multiple doses per day. DFF ¶ 816.

166. As such, the '358 patent discloses a method of treating psoriasis in a patient through administration of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. DFF ¶ 817.

167. Further, a POSA reading the '358 patent would immediately envisage a method of treating psoriasis in a patient through administration of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. DFF ¶ 818.

168. Therefore, the '358 patent discloses "a method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-

acetylaminoisoindoline-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose," as recited in the asserted claim of the '536 patent. DFF ¶¶ 809-820.

169. Therefore, the court concludes that claim 6 of the '536 patent is anticipated by the '358 patent by clear and convincing evidence. DFF ¶¶ 809-820.

F. The Asserted Claim Of The '536 Patent Is Invalid For Obviousness.

170. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); *see also KSR*, 550 U.S. at 427 ("the results of ordinary innovation are not the subject of exclusive rights under the patent laws"). Where the patent is directed to a new treatment using a known compound, it is reasonable to assume that compounds with shared common properties are apt to share other related properties as well. *Anacor Pharms., Inc.*, 889 F.3d at 1384.

171. "Obviousness under 35 U.S.C. § 103(a) is ultimately a legal question, based on underlying factual determinations." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008). "The factual determinations underpinning the legal conclusion of obviousness include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness." *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)).

172. A patent is invalid if it is proven to be obvious by clear and convincing evidence. *See, e.g.*, *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014); *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 993–94 (Fed. Cir. 2009).

173. Obviousness is demonstrated when "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble*, 566 F.3d at 994.

174. In determining the differences between the claimed invention and the prior art, obviousness is judged under "an expansive and flexible approach" driven by "common sense." *KSR*, 550 U.S. at 401, 403; *see also id.* at 421 (finding that the Federal Circuit "drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias," because "[r]igid preventative rules that deny factfinders recourse to common sense . . . are neither necessary under our case law nor consistent with it."); *Senju Pharm. Co. Ltd. v. Apotex Inc.*, 836 F. Supp. 2d 196, 208 (D. Del. 2011) ("The Supreme Court has emphasized the need for courts to value common sense over rigid preventative rules . . . .") (citation omitted).

175. In making this determination, the court must consider both the claimed invention and the prior art as a whole in light of the court's construction of the claims at issue. *See Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479-80 (Fed. Cir. 1998) ("In determining obviousness, the invention must be considered as a whole and the claims must be considered in their entirety.").

176. "For obviousness, a single reference need not disclose every element of the claimed invention." *See, e.g.*, *Hospira, Inc. v. Amneal Pharm., LLC*, 285 F. Supp. 3d 776, 783 (D. Del. 2018) (citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

177. "While it may be easier to prove obviousness if each limitation of the claimed invention is found in the prior art, the level of skill of one of ordinary skill in the art can, at times, fill in the gap when limitations of the claimed invention are not specifically found in the prior art." *Belden Techs.*, 802 F. Supp. 2d at 563.

178. A conclusion of obviousness may be based on a single reference or a combination of prior art references. *See Senju Pharm.*, 836 F. Supp. 2d at 208 ("[A] defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed."); *see also In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("We see no clear error in the Board's determination as to the teachings of the prior art references, in combination.").

179. Where the issue of obviousness is based on a combination of elements, a claim is invalid for obviousness if "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention." *Pfizer*, 480 F.3d at 1361.

180. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416; *see also Q.I. Press Controls, B.V. v. Lee*, 752 F.3d 1371, 1379 (Fed. Cir. 2014) (same). This is because "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *KSR*, 550 U.S. at 402; *id.* at 427 ("We build and create by bringing to the tangible and palpable reality around us new works based on instinct, simple logic, ordinary inferences, extraordinary ideas, and sometimes even genius. These advances, once part of our shared knowledge, define a new threshold from which innovation starts once more. And as progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws.").

181. "Obviousness exists when 'a finite, and in the context of the art, small or easily traversed, number of options . . . would convince an ordinarily skilled artisan of obviousness.'" *Purdue Pharma*, 642 F. Supp. 2d at 368 (*quoting Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)); *see also C.W. Zumbiel*, 702 F.3d at 1387 (finding obviousness where the invention involved "no more than the exercise of common sense in selecting one out of a finite—indeed very small—number of options"). In such a case, an invention is considered "obvious to try." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1332 (Fed. Cir. 2014) (finding claimed dosage obvious to try). Further, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill." *KSR*, 550 U.S. at 401. "When the prior art provides the means of making the invention and predicts the results, and the patentee merely verifies the expectation through 'routine testing,' the claims are obvious." *Purdue*, 642 F. Supp. 2d at 368 (*citing Pfizer*, 480 F.3d at 1367).

182. "Obviousness does not require absolute predictability of success"; rather, "[a]ll that is required is a reasonable expectation of success" in making the invention via the combination. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation omitted); *see also Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 Fed. Appx. 289, 294 (Fed. Cir. 2011) ("[T]here is no requirement that a teaching in the prior art be scientifically tested or even guarantee success before providing a reason to combine. Rather, it is sufficient that one of ordinary skill in the art would perceive from the prior art a reasonable likelihood of success.") (citations omitted).

183. The Federal Circuit "has long rejected a requirement of '[c]onclusive proof of efficacy' for obviousness." *Acorda*, 903 F.3d at 1333 (and cases cited therein).

184. Requiring testing for every possible configuration or combination in the prior art "improperly equates a reasonable expectation of success with absolute certainty." *See, e.g.*, *Hospira*, 285 F. Supp. 3d at 794 (citation omitted).

185. Prior to *KSR*, the Federal Circuit imposed a rigid "teaching-suggestion-motivation" test for obviousness. Under this test, the patent challenger was required to prove that "some motivation or suggestion to combine the prior art teachings" could be found "in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art." *KSR*, 550 U.S. at 407. The Supreme Court in *KSR* rejected the Federal Circuit's test in favor of a more flexible obviousness standard, stating that "the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

186. Under general obviousness analysis, the Court only must weigh whether the prior art would have led to the claimed subject matter using the flexible approaches set forth by the Supreme Court in *KSR*. *See Aventis Pharma*, 499 F.3d at 1301 ("Requiring an explicit teaching to purify the 5(S) stereoisomer from a mixture in which it is an active ingredient is precisely the sort of rigid application of the TSM [teaching, suggestion, motivation] test that was criticized in *KSR*."). Moreover, as noted by the Supreme Court in *KSR* the standard for obviousness does not require absolute predictability of success, only a reasonable expectation given the knowledge and experience of a POSA. *KSR*, 550 U.S. at 420.

187. This more flexible standard expands the obviousness analysis beyond just "published articles and the explicit content of issued patents." *Id.* at 419. In broad terms, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420; *see also Perfect Web Tech., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1329 (Fed. Cir. 2009) ("We therefore hold that . . . an analysis of obviousness . . . may include recourse to logic, judgment, and common sense available to the person of ordinary skill that do not necessarily require explication in any reference or expert opinion.").

188. Courts have sought to determine whether "a person of ordinary skill, before the time of invention and without knowledge of that invention, would have found the invention merely an easily predictable and achievable variation or combination of the prior art." *Rolls-Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1338 (Fed. Cir. 2010). If so, then the invention likely would have been obvious. *Id.* (citation omitted). "To preclude hindsight," the courts will take into account "evidence from before the time of the invention in the form of some teaching, suggestion, or even mere motivation . . . to make the variation or combination." *Id.* (citations omitted).

189. "[A] suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather 'may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.'" *Pfizer*, 480 F.3d at 1362 (Fed. Cir. 2007) (quoting *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).

190. "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *Id.* "[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute." *Life Techs., Inc. v. Clontech Lab., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000); *see also Std. Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("[O]ne should not go about determining obviousness under § 103 by inquiring into what patentees . . . would have known or would likely have done"). The inquiry into whether prior art teachings would have rendered the claimed invention obvious to one of ordinary skill in the art, is, as a matter of law, "independent of the motivations that led the inventors to the claimed invention." *Life Techs.*, 224 F.3d at 1325.

191. "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claim." *KSR*, 550 U.S. at 419-20; *see also Norgren Inc. v. ITC*, 699 F.3d 1317, 1324-26 (Fed. Cir. 2012) (affirming invalidity of claims under § 103 where the claimed invention solved known problems by the use of an obvious solution). Even more, the discovery of a problem does not always result in a patentable invention. *Norgren*, 699 F.3d at 1327. For instance, an alleged invention is obvious in view of "evidence of known problems and an obvious solution." *Id.* Where a claim "simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 417 (quotation omitted).

192. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious. *KSR*, 550 U.S. at 421.

193. "When a work is available in one field, design incentives and other market forces can prompt variations of it, either in the same field or in another. If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability. Moreover, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill." *KSR*, 550 at 401.

194. None of "the length, expense, [or] difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably 'routine' to one of ordinary skill in the art." *Pfizer*, 480 F.3d at 1367.

195. A "claim to a product does not become nonobvious simply because the patent specification provides a more comprehensive explication of the known relationships between the variables and the affected properties." *In re Applied Materials, Inc.*, 692 F.3d at 1297.

196. Even if a reference does not rise to the level of prior art, a court may consider it as motivation to combine. *See, e.g.*, *Lucent Techs., Inc. v. Gateway, Inc.*, 537 F. Supp. 2d 1095, 1102 (S.D. Cal. 2008) (*citing Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1337-38 (Fed. Cir. 2004)).

197. The motivation to combine inquiry is not limited to what products are forthcoming or currently available on the market, particularly given the lengthy FDA approval process. *Bayer*, 874 F.3d at 1324; *see also id.* at 1326 ("'Motivation to combine may be found in many different places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications.'") (quoting *Allergan*, 726 F.3d at 1292). "Obviousness does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art does not teach away." *Id.* at 1328 (emphasis in original).

198. A *prima facie* case of obviousness exists where a claimed range and a prior art range are overlapping. *Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1311 (Fed. Cir. 2006). A *prima facie* case of obviousness further exists even where the claimed range and a prior range are not directly overlapping but are nevertheless close enough that one skilled in the art would have expected them to have the same properties. *See, e.g.*, *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 782-83 (Fed. Cir. 1985) (affirming a rejection of a claim directed to an alloy "having 0.8% nickel, 0.3% molybdenum, up to 0.1% maximum iron, balance titanium" as obvious over a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31 molybdenum, balance titanium).

199. "To establish obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014); *see also Mead Johnson & Co. v. Premo Pharm. Labs*, No. 75-1230, 1980 U.S. Dist. LEXIS 15750, *103-04 (D.N.J. 1980). "Generally, an obviousness inquiry concerning such 'known compounds' focuses on the identity of a 'lead compound.'" *Bristol-Myers Squibb*, 752

F.3d at 973. "The motivation to modify that lead compound can come from any number of sources and need not necessarily be explicit in the art." *Id.*

200. The Federal Circuit's "lead compound test" applies only in one special situation, the determination of obviousness for a novel pharmaceutical compound, *i.e.*, a compound that was never previously disclosed in the prior art in any form. *See Novartis Pharm. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1059-60 (Fed. Cir. 2019).

201. The Federal Circuit's lead compound test examines whether a POSA would have had both: (1) a reason to select a lead compound—a compound with particular utility or properties of pharmacological interest—from the various compounds disclosed in the prior art; and (2) a motivation to make chemical modifications to that lead compound by adding or subtracting an atom or groups of atoms that would have resulted in the claimed compound. *See id*. at 1060 (finding that the District Court erred in applying the lead compound test to a method of treatment claim discussing a compound disclosed in the prior art).

202. The Federal Circuit has declined to extend this special test to the situation at bar, the separation of enantiomers from a disclosed racemate, because that encompasses a physical separation of the disclosed components of the racemic mixture. *See Aventis Pharma*, 499 F.3d at 1301-03; *see also UCB, Inc. v. Accord Healthcare, Inc*., 890 F.3d 1313, 1328-29 (Fed. Cir. 2018) (declining to apply lead compound test to claim to enantiomers when racemate had been disclosed in the prior art). The separation process includes no chemical modification of any compound because the chemical components of the enantiomers are not different when present in the racemic mixture or isolated in a more purified form.

203. A "lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound." *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d

1346, 1354 (Fed. Cir. 2010). Rather, any known compound that has "promising useful properties" can be a lead compound that would have motivated "a chemist to make structurally similar compounds." *Id.*; *see also Altana*, 566 F.3d at 1008 ("[T]o the extent Altana suggests that the prior art must point to only a single lead compound for further development efforts, that restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR*.").

204. Conversely, the fact that many other compounds also could have been selected does not diminish the motivation to select a particular lead compound. *See id.* ("Altana suggests that the prior art would not have directed one of skill in the art to select compound 12 over the approximately 90 compounds claimed to be improvements in . . . prior art patents, or, for that matter, over the thousands of other compounds included in the prior art disclosures. . . . [T]he district court had a sufficient evidentiary basis for rejecting that position.").

205. In *UCB*, the district court found that a purified enantiomer was not obvious in light of the prior art disclosure of its racemate under a lead compound analysis focused on evaluation of pharmacological data and beneficial properties compared to other prior art compounds disclosed by the same inventors. *See UCB*, 890 F.3d at 1328-29. On appeal, the Federal Circuit affirmed the district court's holding but refused to require use of the lead compound test, noting that *Aventis* is the governing standard for claims to purified enantiomers, which only requires a motivation to purify the known mixture based on some desirable property. *Id*. at 1329. The *UCB* court found that even under *Aventis* "no clear error" existed in the district court's ultimate holding because there was no teaching in the prior art that the racemate had any beneficial properties or that the racemate could or should be separated into its enantiomers. *Id*. at 1328-29. Instead, the Federal Circuit noted the prior art taught that the racemate had inferior

properties to other compounds identified by the inventors in their prior art patents and publications. *Id*.

206. An analysis selecting a lead chemical compound is not required to find obviousness, when the relevant chemical compound is known in the prior art. *See generally Pfizer*, 480 F.3d 1348 (finding obviousness of a claim directed to amlodipine besylate, where amlodipine was claimed in the prior art); *see also Novartis Pharm. Corp. v. West-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1060 (Fed. Cir. 2019) (where the patent-in-suit claimed a method of using the compound everolimus, the case did "not require lead compound analysis or analysis of whether a particular dose in a range of prior art doses would have been obvious", stating that "[t]o the extent the district court required a showing that a person of ordinary skill would have selected everolimus over other prior art compounds, it erred.").

207. The Federal Circuit has held that analyzing whether a prior art reference is enabling of the claimed subject matter has no place in an obviousness analysis. *See Raytheon Techs. Corp. v. Gen. Elec. Co.*, 993 F.3d 1374, 1380 (Fed. Cir. 2021) ("While a reference must enable someone to practice the invention in order to anticipate under § 102(b), a non-enabling reference may qualify as prior art for the purpose of determining obviousness under § 103.") (citing *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578 (Fed. Cir. 1991)); *Beckman*, 892 F.2d at 1551 ("Even if a reference discloses an inoperative device, it is prior art for all that it teaches.").

1. Claim 6 Of The '536 Patent Is Obvious Over The '358 Patent And WO '606 In View Of Dyke 1999 And Marriott 2001 And The Knowledge Of A POSA.

a. Stereomerically Pure (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione That Comprises Greater Than About 97% By Weight Of (+) Isomer

Is Obvious Over The '358 Patent And WO '606 And The Knowledge Of A POSA.

208. As set forth above, the Court finds that "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," and "a pharmaceutically acceptable salt thereof," as recited in the asserted claims of the '638 patent, are obvious over the '358 patent in combination with WO '606 and the knowledge of a POSA. DFF ¶ 821.

209. For all the same reasons set forth above, the Court concludes that the following claim limitations are obvious over the '358 patent in combination with WO '606 and the knowledge of a POSA: "stereomerically pure compound comprises greater than about 97% by weight of (+) isomer," as recited in claim 6 of the '536 patent. DFF ¶ 822.

b. The Method Of Treatment Limitations In Claim 6 Of The '536 Patent Are Obvious Over The '358 Patent In View Of Dyke 1999 And Marriott 2001 And The Knowledge Of A POSA.

i. Motivation.

210. It was known prior to 2002 that increased levels of TNFα, a proinflammatory cytokine, are involved in the pathogenesis of inflammatory skin conditions, such as psoriasis, and thus a POSA would have been motivated to target this pathway in finding an alternative treatment for such diseases. DFF ¶ 825.

211. The '358 patent discloses compounds of "Formula I," including apremilast, and their use in inhibiting phosphodiesterases, particularly PDE4, and in the treatment of diseases mediated by inhibition of PDE4. The '358 patent discloses that decreasing TNFα levels, increasing cAMP levels, and inhibiting PDE IV thus constitute valuable therapeutic strategies for the treatment of many inflammatory, infectious, immunological or malignant diseases, including psoriasis and rheumatoid arthritis. DFF ¶ 828.

212. The '358 patent teaches dosage forms and dose amounts for the compounds of "Formula I," including apremilast, that are therapeutically effective for treating diseases that are ameliorated by the inhibition of PDE4. In particular, the '358 patent provides that such compounds can be administered orally, rectally, or parenterally, alone or in combination with other therapeutic agents including antibiotics, steroids, etc., to a mammal in need of treatment. DFF ¶ 830.

213. The '358 patent further discloses oral dosage forms, including tablets and capsules containing from 1 to 100 mg of drug per unit dosage. The '358 patent discloses that the compositions can be formulated into:

> physically discrete units suitable as a unitary dosage, or a predetermined fraction of a unitary dose to be administered in a single or multiple dosage regimen to human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with a suitable pharmaceutical excipient.

A POSA would have understood the '358 patent's teaching that the compositions can be administered in a single or multiple dosage regimen to human subjects and other mammals to mean once, twice, or three times daily. The '358 patent also states that pharmaceutical compositions thus comprise one or more compounds of the present invention associated with at least one pharmaceutically acceptable carrier, diluent or excipient. The '358 patent provides that the pharmaceutical compositions can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders. In Examples 22-25, exemplary tablets were prepared containing 100 mg, 75 mg, 10 mg, and 100 mg, respectively, of the active ingredient. DFF ¶ 831.

214. Dyke 1999 discloses that a number of groups have investigated the effect of PDE4 inhibitors on skin. These studies showed that the PDE4 inhibitor, Ro20-1724 led to a

three-fold increase in cAMP concentrations in epidermal cells, thereby suggesting that PDE4 inhibitors may be potentially beneficial in psoriasis. PDE4 inhibitors were also shown to inhibit the inflammatory response of a number of mediators *via* either topical or systemic administration. In addition, Dyke 1999 provides that Ro20-1724 was investigated clinically in two double-blind studies comparing its effectiveness to vehicle. The results from the clinical study showed that PDE4 inhibition improved psoriatic lesions and had no adverse systemic or cutaneous effects, again, suggesting the therapeutic potential of such compounds in the treatment of psoriasis. DFF ¶ 843.

215. The Court finds, in light of the teachings of the '358 patent and Dyke 1999 regarding the therapeutic potential of PDE4 inhibition for treating inflammatory diseases like psoriasis, a POSA would have further looked to Marriott 2001, which confirms that thalidomide analogs were known to be potent PDE4 inhibitors. DFF ¶ 844.

216. Marriott 2001 further confirms the teachings of the '358 patent that thalidomide analogs, such as (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, can potently inhibit PDE4 and are therapeutically useful for treating a wide range of inflammatory diseases, such as psoriasis. In light of the teachings of the '358 patent, in view of Dyke 1999 and Marriott 2001, a POSA would have been motivated to further develop thalidomide analogs with PDE4 inhibitory activity to treat psoriasis, with a reasonable expectation of success. DFF ¶ 851.

217. The Court concludes that a POSA would have been motivated to combine the '358 patent with Dyke 1999 and Marriott 2001, as each of these references discuss PDE4 inhibiting compounds for the treatment of inflammatory conditions, including psoriasis. DFF ¶ 852.

ii. Reasonable Expectation Of Success.

218. The '358 patent disclosed and/or taught steromerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, its use in the inhibition of PDE4, and the treatment of diseases mediated by PDE4 inhibition, including psoriasis. A POSA reviewing Dyke 1999 would have known that PDE4 inhibitors had been demonstrated to have anti-inflammatory effects, given that inhibition of PDE4 results in the elevation of cAMP, which thereby decreases the release of TNF-α from macrophages and monocytes. Dyke 1999 also taught the use of PDE4 inhibitors in the treatment of rheumatoid arthritis and that these compounds had the potential to treat psoriasis. DFF ¶ 853.

219. A POSA would have known that PDE4 had been implicated in the pathogenesis of inflammatory diseases and that PDE4 was present in the majority of inflammatory cells. A POSA would have also been well aware that selective PDE4 inhibitors had broad anti-inflammatory activity and could suppress the release of a range of inflammatory mediators from inflammatory cells. Therefore, a POSA would have been motivated to develop selective PDE4 inhibitors to treat a wide range of inflammatory diseases. DFF ¶ 854.

220. A POSA also would have known that psoriasis is an inflammatory disease and is characterized by hyperproliferation of keratinocytes. Further, a POSA would have known that psoriasis is associated with an excessive release of inflammatory mediators, particularly TNF-α. A POSA would also have known that levels of TNF-α produced by PBMC obtained from psoriasis patients showed that TNF-α produced by these cells is significantly higher compared to the levels produced by PBMC obtained from healthy subjects. Therefore, a POSA would have been motivated to reduce levels of TNF-α in a person with psoriasis, to contribute to an anti-inflammatory effect. DFF ¶ 855.

221. A POSA reading Marriott 2001 would have known that thalidomide was an established anti-inflammatory drug with potential use in treating various conditions including rheumatoid arthritis and that a subset of thalidomide analogues called SelCIDs were PDE4 inhibitors and could have been used to inhibit TNF-α. As a POSA would have known that PDE4 inhibitors could treat rheumatoid arthritis through inhibition of TNF-α, as well as potentially treat the inflammatory condition psoriasis, a POSA would have been motivated to use (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (a PDE4 inhibitors disclosed in the '358 patent) to treat such psoriasis. DFF ¶ 856.

222. The Court finds, based on the foregoing, a POSA reading the '358 patent, in view of Marriott 2001 and Dyke 1999, and in view of the POSA's knowledge, would have been motivated, with a reasonable expectation of success, to treat psoriasis in a patient through administration of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. DFF ¶ 857.

223. Therefore, the Court concludes that "a method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose," as recited in asserted claim 6 of the '536 patent, is obvious over of the '358 patent and WO '606 in view of Dyke 1999 and Marriott 2001, and the knowledge of a POSA, by clear and convincing evidence, and a POSA would have been motivated with a reasonable expectation of success to practice the method of claim 6. DFF ¶ 858.

2. Claim 6 Of The '536 Patent Is Obvious Over The '358 Patent And Takeuchi In View Of Dyke 1999 And Marriott 2001 And The Knowledge Of A POSA.

a. The Stereomerically Pure (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione That Comprises Greater Than About 97% By Weight Of (+) Isomer Is Obvious Over The '358 Patent And Takeuchi And The Knowledge Of A POSA.

224. As set forth above, the Court finds that "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," and "a pharmaceutically acceptable salt thereof," as recited in the asserted claims of the '638 patent, are obvious over the '358 patent in combination with Takeuchi and the knowledge of a POSA. DFF ¶ 859.

225. For all the same reasons set forth above, the Court concludes that the following claim limitations are obvious over the '358 patent in combination with Takeuchi and the knowledge of a POSA: "stereomerically pure compound comprises greater than about 97% by weight of (+) isomer," as recited in claim 6 of the '536 patent. DFF ¶ 860.

b. The Method Of Treatment Limitations In Claim 6 Of The '536 Patent Are Obvious Over The '358 Patent In View Of Dyke 1999 And Marriott 2001, And The Knowledge Of A POSA.

226. For the same reasons discussed above, a POSA reading the '358 patent, in view of Marriott 2001 and Dyke 1999, and in view of the POSA's knowledge, would have been motivated, with a reasonable expectation of success, to treat psoriasis in a patient through administration of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. DFF ¶ 861.

227. A POSA reading the '358 patent, in view of Marriott 2001 and Dyke 1999, and in view of the POSA's knowledge, would have been motivated, with a reasonable expectation of

success, to treat psoriasis in a patient through administration of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. DFF ¶ 861.

228. Therefore, the Court concludes that "a method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose," as recited in asserted claim 6 of the '536 patent, is obvious over of the '358 patent and Takeuchi in view of Dyke 1999 and Marriott 2001, and the knowledge of a POSA, by clear and convincing evidence, and a POSA would have been motivated with a reasonable expectation of success to practice the method of claim 6. DFF ¶¶ 859-862.

3. Claim 6 Of The '536 Patent Is Obvious Over The '358 Patent In View Of Dyke 1999, Marriott 2001, And Muller 1998, And The Knowledge Of A POSA.

a. The Stereomerically Pure (+)-2-[1-(3-Ethoxy-4-Methoxyphenyl)-2-Methylsulfonylethyl]-4-Acetylaminoisoindoline-1,3-Dione That Comprises Greater Than About 97% By Weight Of (+) Isomer Is Obvious Over The '358 Patent And The Knowledge Of A POSA.

229. As set forth above, the Court finds that "stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione," and "a pharmaceutically acceptable salt thereof," as recited in the asserted claims of the '638 patent, are disclosed in the '358 patent. DFF ¶ 863.

230. For all the same reasons set forth above, the Court concludes that the following claim limitations are disclosed in the '358 patent: "stereomerically pure compound comprises

greater than about 97% by weight of (+) isomer," as recited in claim 6 of the '536 patent. DFF ¶ 864.

b. The Method Of Treatment Limitations In Claim 6 Of The '536 Patent Are Obvious Over The '358 Patent In View Of Dyke 1999, Marriott 2001, And Muller 1998, And The Knowledge Of A POSA.

i. Motivation.

231. For the same reasons discussed above, a POSA would have been motivated to further develop thalidomide analogs with PDE4 inhibitory activity to treat psoriasis, with a reasonable expectation of success, in light of the teachings of the '358 patent, in view of Dyke 1999 and Marriott 2001. DFF ¶¶ 865.

232. A POSA would have been motivated to combine the '358 patent with Dyke 1999, Marriott 2001, and Muller 1998, as each of these references discuss PDE4 inhibiting compounds. DFF ¶ 867.

ii. Reasonable Expectation Of Success.

233. A POSA reading Marriott 2001 would have known that thalidomide was an established anti-inflammatory drug with potential use in treating various conditions including rheumatoid arthritis and that a subset of thalidomide analogues called SelCIDs were PDE4 inhibitors and could have been used to inhibit TNF-α. Muller 1998 would have further confirmed that thalidomide analogues inhibit PDE4 and therefore inhibit production of TNF-α and disclosed that excessive TNF-α levels were associated with inflammatory conditions such as rheumatoid arthritis. As a POSA would have known that PDE4 inhibitors could treat rheumatoid arthritis through inhibition of TNF-α, as well as potentially treat the inflammatory conditions psoriasis, a POSA would have been motivated to use (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-

methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione (a PDE4 inhibitor disclosed in the '358 patent) to treat psoriasis. DFF ¶ 868.

234. Based on the foregoing, a POSA reading the '358 patent, in view of Marriott 2001, Dyke 1999, and Muller 1998, and in view of the POSA's knowledge, would have been motivated, with a reasonable expectation of success, to treat inflammatory diseases, including diseases or disorders ameliorated by the inhibition of PDE4 (such as psoriasis and the arthritic condition psoriatic arthritis), in a patient through administration of stereomerically pure (+)-2-[1-(3-Ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione. DFF ¶ 869.

235. Therefore, "a method of treating psoriasis, which comprises orally administering to a patient having psoriasis about 10 mg to about 200 mg per day of stereomerically pure (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione, wherein the compound is administered in the form of a tablet or capsule as either a single dose or a divided dose," as recited in the asserted claim of the '536 patent is obvious over of the '358 patent in view of Dyke 1999, Marriott 2001, and Muller 1998, and the knowledge of a POSA, by clear and convincing evidence, and a POSA would have been motivated with a reasonable expectation of success to practice the method of claim 6. DFF ¶¶ 863-870.

236. At trial, Amgen's expert Dr. Knowles argued that a POSA would not have reasonably expected apremilast to be successful in treating psoriasis, as required by claim 6 of the '536 patent, given the lack of data in the prior art regarding the safety or tolerability of apremilast and for a POSA "to really be sure" whether a thalidomide analog like apremilast "would work or not." DFF ¶ 871. To be sure, "[o]bviousness does not require absolute predictability of success," but rather, only a "reasonable expectation of success." *Medichem*, 437

F.3d at 1165. Thus, obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364 (quotations omitted). The Court finds that the prior art available as of the 2002 priority date would have provided a POSA with a reasonable expectation of success in using apremilast to treat a patient suffering from an inflammatory condition such as psoriasis.

237. In any event, the Court does not find Amgen's persuasive because the '536 patent itself provides no data to support the administration of 10-200 mg of apremilast to a patient for the treatment of psoriasis. It "would constitute clear error for the court to discredit the [prior art] for the same lack of dosing [] clinical data from which the ['536 patent] suffer[s]." *In re Copaxone Consolidated Cases*, Civ. Action No. 14-1711-GMS, 2017 WL 401943, at *17 (D. Del. Jan. 30, 2017). Amgen's expert, Dr. Alexis, does not dispute that the specification of the '536 patent does not disclose which, if any, doses of apremilast are safe and effective for administration to patients with psoriasis. DFF ¶ 872. Nor is there any dispute that the '536 patent fails to disclose any clinical data supporting the safety and efficacy of apremilast, at any of the claimed doses, for treating psoriasis in a patient. *Id.* Thus, the "claimed invention adds nothing beyond the teachings of" the prior art, and the Court will not find any "difference[s] between the claimed invention and the [prior art] on this point." *Merck & Co., Inc. v. Teva Pharms USA, Inc.*, 395 F.3d 1364, 1374 (Fed. Cir. 2005) (finding clear error where the district court held that the claimed method nonobvious because the prior art failed to explain how a higher once-weekly dosing regimen would avoid dose-related adverse events, when the asserted patent "sets forth no human clinical or laboratory data showing the safety and tolerability of the treatment methods claimed by the patent").

III. Objective Indicia Of Nonobviousness Support A Finding Of Obviousness For The '638 And '536 Patents.

238. The Court finds no evidence of secondary considerations of non-obviousness that overcome the *prima facie* cases of obviousness for the '638 and '536 patents discussed above.

239. Amgen's experts raise a variety of purported objective indicia of nonobviousness, none of which, alone or in combination, casts doubt on or overcomes the obviousness of the '638 or the '536 patent. Amgen must present evidence to support a finding that a given secondary consideration exists by a preponderance of the evidence. *See, Apple Inc. v. Samsung Elec. Co., Ltd.*, 839 F.3d 1034, 1053 (Fed. Cir. 2016). To have relevance and substantial weight in the validity analysis, the patentee must show with factual evidence that any asserted secondary considerations have a "nexus" between the consideration and the novel features of the claimed invention. *See, e.g., In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011) ("Where the offered secondary consideration actually results from something other than what is both claimed and novel in the claim, there is no nexus to the merits of the claimed invention.").

240. Even when there is a showing of objective indicia of non-obviousness, it still can be insufficient to rebut a clear showing of obviousness. *See Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364-65 (Fed. Cir. 2012). Where "a claimed invention represents no more than the predictable use of prior art elements according to established functions . . . evidence of secondary indicia are frequently deemed inadequate to establish non-obviousness." *Ohio Willow Wood Co. v. Alps S., LLC*, 735 F.3d 1333, 1344 (Fed. Cir. 2013).

241. In addition, the entire discussion of long-felt but unmet need, clinical success, failure of others, and commercial success is legally flawed as it must be viewed with the knowledge that there was a blocking patent—the '358 patent—which served as a significant disincentive to others who may have been interested in developing and commercializing

apremilast. *Acorda*, 903 F.3d at 1339. Moreover, Amgen's alleged evidence of secondary considerations "actually results from something *other* than what is both claimed and *novel* in the [asserted] claim [of the '536 patent], [so] there is no nexus to the merits of the claimed invention." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1385 (Fed. Cir. 2015).

A. The Therapeutic Index Of Apremilast Does Not Support Nonobviousness.

1. Amgen's Therapeutic Index Of 12 For Apremilast Was Calculated In Celgene's Confidential Study And Uses Only Emetic Episodes As The Relevant Side Effect.

242. Amgen's experts discussed a value of 12 for the therapeutic index of apremilast by relying on a confidential Celgene Study Report titled "Therapeutic Index of SelCIDs in Ferret Lung Neutrophilia and Emesis Model." DFF ¶ 1010. In the ferret model discussed in Celgene's Study Report ("Celgene's Ferret Study"), apremilast's therapeutic index of 12 takes into account only one side effect (i.e., emetic episodes), and it does not account for other side effects. DFF ¶¶ 1010-1048. For these reasons, the Court finds apremilast's therapeutic index of 12 is not persuasive evidence of secondary considerations. *See Aventis Pharma S.A. v. Hospira, Inc.*, 743 F. Supp. 2d 305, 348 (D. Del. 2010) ("the patent owner must first show what properties were expected" by a POSA at the time of invention) (citation omitted); *see also In re Kahn*, 441 F.3d 977, 990-91 (Fed. Cir. 2006) (establishing long-felt, unmet need "requires that the applicant submit actual evidence of long- felt need, as opposed to argument").

2. The Therapeutic Index Of 12 Is Based Only On The Side Effect Of Emetic Episodes And Does Not Take Into Account Other Relevant Side Effects..

243. Apremilast's therapeutic index of 12 in Celgene's Ferret Study only used emetic episodes as an endpoint, did not take nausea into account, and was therefore flawed. DFF ¶¶ 1027-1040.

244. There is no single therapeutic index value for one drug, as the value of the therapeutic index depends on what side effect is used as the relevant endpoint. DFF ¶¶ 1004-1005, 1027-1040.

245. Therefore, the Court concludes that a therapeutic index of 12 for apremilast in Celgene's Ferret Study using only emetic episodes as the relevant side effect is not persuasive evidence of Amgen's (and Dr. Knowles's) asserted secondary considerations. DFF ¶¶ 1001-1048.

B. There Is No Evidence Of Unexpected Results That Supports The Non-Obviousness Of The Asserted Claims Of The '638 And The '536 Patents.

1. There Is No Evidence Of Unexpected Results Based On Comparison Of Apremilast To Cilomilast, Based On Their Therapeutic Indices In Celgene's Ferret Study.

246. Whether there are unexpected results is a question of fact. *See, e.g., In re Peterson,* 315 F.3d 1325, 1331 (Fed. Cir. 2003). An invention that otherwise appears obvious from the prior art may, in certain circumstances, not be obvious if the evidence (not conclusory statements or argument) shows that the claimed invention produces some superior property or advantage that was unexpected by or surprising to a POSA at the time of the invention. *See, e.g., Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, Case No. 14-cv-882-LPS, 2017 WL 1199767, at *39 (D. Del. Mar. 31, 2017), *aff'd*, 903 F.3d 1310, 1341 (Fed. Cir. 2018); *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) ("To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention.").

247. The relevant time-period for the "unexpected results" inquiry is whether the results would have been unexpected by one of ordinary skill in the art at the time of the

patentee's application and based on knowledge available at that time. *See, e.g., In re Geisler,* 116 F.3d 1465, 1470 (Fed. Cir. 1997); *Pfizer Inc. v. Teva Pharm. USA, Inc.,* 460 F. Supp. 2d 659, 667 (D.N.J. 2006) ("[S]everal cases . . . preclude reliance by an inventor or patentee on undisclosed, later-discovered advantages."). This showing requires "factual evidence," not merely the unsupported assertions of counsel. *In re Youngblood,* No. 98-1518, 1999 WL 504243, at *7 (Fed. Cir. 1999) (deeming unsupported assertions "insufficient"). And any evidence that is in fact provided should be "weighed against contrary evidence indicating that the results were not unexpected or not a substantial improvement over the prior art." *Santarus Inc. v. Par Pharm., Inc.,* 720 F. Supp. 2d 427, 457 (D. Del. 2010).

248. Any superior property or advantage must be unexpected at the time the application was filed and the court should consider what properties were expected by a POSA. *See, e.g., Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007) ("[I]n order to properly evaluate whether a superior property was unexpected, the court should have considered what properties were expected."). A patentee fails to show unexpected results if there is no evidence of what the POSA would have expected at the time of the invention. *Aventis,* 743 F. Supp. 2d at 348 ("the patent owner must first show what properties were expected") (citation omitted).

249. Evidence of unexpected results must make a comparison of the results achieved by the claimed invention with the results from the closest prior art. *See, e.g., Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1363 (Fed. Cir. 2012) ("Wrigley needed to demonstrate that the results were unexpected to a significant degree beyond what was already known about the effect of combining" the prior art); *In re DeBlauwe*, 736 F.2d 699, 705 (Fed. Cir. 1984); *In re Johnson,* 747 F.2d 1456, 1460 (Fed. Cir. 1984).

250. A party advancing evidence of unexpected results must therefore provide evidence of what would have been expected by a skilled artisan. *Pfizer,* 480 F.3d at 1371. Only by comparison to what would have been expected can the patentee then show that its claimed invention has superior properties that were unexpected. *Id.*

251. To be probative in the validity inquiry, the supposedly unexpectedly superior result must be "different in kind and not merely in degree from the results in the prior art." *Galderma Labs., L.P. v. Tolmar, Inc.,* 737 F.3d 731, 739 (Fed. Cir. 2013).

252. Like other secondary considerations, unexpected results may be insufficient to rebut a finding of obviousness.

253. Dr. Knowles conclusorily testified that a POSA would not have expected a 31-fold improvement in the therapeutic index for apremilast as compared to cilomilast in Celgene's Ferret Study. DFF ¶ 1093. Dr. Knowles also offered a conclusory opinion that "apremilast is only apremilast if it's essentially pure." DFF ¶ 1093.

254. As an initial matter, the Court finds cilomilast is not the closet prior art to the asserted claims of the '638 and '536 patents. DFF ¶ 1094. *See In re Merck*, 800 F.2d 1091, 1098-99 (Fed. Cir. 1986). Amgen can identify no legal authority that permits substituting other compounds for the closest prior art simply because a document (the '358 patent) does not disclose some details (specifically, pharmacological data) or because the closest prior art compound was not commercially available. *See Trustees of Columbia Univ. v. Illumina, Inc.*, 620 F. App'x 916, 932 (Fed. Cir. 2015) ("[T]here is no requirement that the closest prior art be commercialized.") (citing *In re Merchant*, 575 F.2d 865, 869 (C.C.P.A. 1978).

255. Dr. Knowles relied on confidential data that a POSA would not have had access to in discussing the therapeutic indices of apremilast and cilomilast. DFF ¶ 1095. *See Aventis*,

743 F. Supp. 2d at 348 ("the patent owner must first show what properties were expected" by a POSA at the time of invention) (citation omitted).

256. Furthermore, apremilast's therapeutic index of 12 in Celgene's Ferret Study does not support unexpected results, due to the problems discussed with this measurement. DFF ¶¶ 1001-1048.

257. To even potentially reach a determination that apremilast was superior to cilomilast, a POSA would need additional data from other experiments that looked at side effects other than emetic episodes, to properly determine the therapeutic windows of apremilast and cilomilast. DFF ¶ 1097.

258. Thus, the Court concludes that a POSA would not determine that apremilast was superior to cilomilast based solely on a 31-fold difference in their therapeutic indices in Celgene's Ferret Study, and this is not evidence of unexpected results. DFF ¶ 1098. *See Galderma Labs.*, 737 F.3d at 739 (to be probative in the validity inquiry, the supposedly unexpectedly superior result must be "different in kind and not merely in degree from the results in the prior art") (quotation and citation omitted).

2. There Is No Evidence Of Unexpected Results Based On Dr. Knowles's Comparison Of Apremilast To The Racemic Mixture (Example 12 Of The '358 Patent) Based On Only Two Data Points.

a. PDE4A4 Ratio.

259. Dr. Knowles relied on Dr. Schafer's testimony that "apremilast had a PDE4A4 ratio that was much lower than that of Example 12." DFF ¶ 1100. Dr. Knowles stated that apremilast exhibited an 11-fold improvement in its PDE4A4 ratio, as compared to Example 12. DFF ¶ 1100. However, this is not persuasive evidence of unexpected results. *See Galderma Labs.*, 737 F.3d at 739 (to be probative in the validity inquiry, the supposedly unexpectedly

superior result must be "different in kind and not merely in degree from the results in the prior art") (quotation and citation omitted).

260. The document disclosing the PDE4A4 ratios discussed by Dr. Knowles was confidential Celgene information. DFF ¶ 1101. The PDE4A4 ratio discussed by Dr. Knowles was an internal Celgene calculation that was not known to the person of ordinary skill in the art. DFF ¶ 1101. *See Aventis*, 743 F. Supp. at 348.

261. Dr. Knowles conclusorily testified that the lower PDE4A4 ratio of apremilast would have been unexpected, simply stating that "[t]here was no data to provide a POSA or anyone else to think that that might be the result." DFF ¶ 1102. The Court finds this conclusory testimony insufficient to show unexpected results.

b. Potency In Celgene's *In Vivo* Mouse Model.

262. Dr. Knowles testified that apremilast exhibited a 20-fold improvement in potency *in vivo* in a mouse model, as compared to Example 12, when measuring inhibition of TNF-α. DFF ¶ 1103. Dr. Knowles conclusorily testified that the POSA would not have expected a 20-fold difference in potency between apremilast and Example 12. DFF ¶ 1103.

263. Dr. Knowles relied on Celgene's confidential internal data which would not have been available to a POSA when comparing the potency data for apremilast and Example 12. DFF ¶ 1104. *See Aventis*, 743 F. Supp. at 348.

264. A POSA would not rely on potency data alone to determine that apremilast was unexpectedly superior to Example 12, and therefore, the Court finds Amgen has not demonstrated evidence of unexpected results. DFF ¶¶ 1105-1108. *See Galderma Labs.*, 737 F.3d at 739 (to be probative in the validity inquiry, the supposedly unexpectedly superior result must be "different in kind and not merely in degree from the results in the prior art") (quotation and citation omitted).

c. Example 12 Had Advanced Into Clinical Studies In Humans.

265. Example 12 was also named "7085" or "CC-7085", "CC-17085", and CDC-998. DFF ¶ 1109.

266. CC-7085 is a racemic mixture, and apremilast is one of the enantiomers that makes up that racemic mixture. DFF ¶ 1110.

267. Example 12 (CC-7085) was advanced into three phase 1 clinical trials in humans. DFF ¶ 1111.

268. Dr. Knowles described a six-step evaluation process for a PDE4 inhibitor or a "cascade of different assays", with those steps being: (1) enzyme assays; (2) cellular assays; (3) *in vivo* animal efficacy and acute tolerability models (including therapeutic index); (4) assessments of physicochemical properties and animal pharmacokinetics; (5) chronic safety studies; and (6) clinical studies in humans. DFF ¶ 1118.

269. When a drug has entered phase 1, phase 2, or phase 3 clinical studies, that drug would have passed through each of steps one through five in Dr. Knowles's drug development cascade. DFF ¶ 1119.

270. Human clinical studies of Example 12 would have occurred in step six of the six-step drug development cascade or evaluation progress of PDE4 inhibitors described by Dr. Knowles. DFF ¶ 1120.

271. Therefore, Example 12 would have shown results satisfactory to Celgene through steps 1-5 of the drug development cascade or PDE4 evaluation process. DFF ¶ 1121.

272. For the foregoing reasons, the Court concludes that Amgen (and Dr. Knowles) have failed to present persuasive evidence of unexpected results. DFF ¶¶ 1093-1122.

C. There Was No Skepticism Regarding Apremilast's Structural Features.

273. Where the record "does not express any direct skepticism concerning the feasibility" of the invention, the "assertion that there were secondary indicia of skepticism that rendered the invention of the asserted claims nonobvious is supported only by evidence that is irrelevant and not supportive." *Dow Jones & Co. v. Ablaise Ltd.,* 606 F.3d 1338, 1352 (Fed. Cir. 2010); *see also Ruiz v. A.B. Chance Co.,* 357 F.3d 1270, 1274-75 (Fed. Cir. 2004) (where the record actually "does not show that [the industry] doubted that [the claimed invention] would work," the evidence of "skepticism of experts [i]s weak").

274. Further, the Federal Circuit has stated that the FDA performing its "normal duties," such as requesting clinical safety data and data demonstrating efficacy benefits, "in no way indicates that the FDA experts would have been surprised to receive such data" and is not evidence of skepticism in support of nonobviousness. *Bayer Healthcare Pharm., Inc. v. Watson Pharm., Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013). Rather, such activities of the FDA are part of its "normal duties ensuring the safety and efficacy of new drugs." *Id.* (DFF ¶¶ 1079-1094.)

275. Substantiating a claim of skepticism of experts often requires a showing of technical infeasibility or manufacturing uncertainty—not economic considerations or other companies' preferences. *See Orthopedic Equip. Co. v. United States,* 702 F.2d 1005, 1013 (Fed. Cir. 1983) ("[T]hat the two disclosed apparatus would not be combined by businessmen for economic reasons is not the same as saying that it could not be done because skilled persons in the art felt that there was some technological incompatibility that prevented their combination."); *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1328 (Fed. Cir. 2008) ("[M]arket-force skepticism also lacks the requisite nexus to the claimed invention."); *AstraZeneca LP v. Breath*

Ltd., 542 Fed. Appx. 971, 980 (Fed. Cir. 2013) ("evidence of corporate prudence" is not "industry skepticism"). (DFF ¶¶ 1079-1094.)

276. The Court finds a POSA would not have been skeptical of apremilast. Apremilast is more structurally different than similar to thalidomide. The only portion of apremilast that is in common with thalidomide is the left-side phthalimid ring and the rest is different. The toxicity of thalidomide as a teratogen is related to the acidic hydrogen on the chiral carbon that causes thalidomide to racemize. Apremilast does not have an acidic hydrogen on its chiral carbon and does not, and would not be expect to, racemize. DFF ¶ 1123-1138.

277. Celgene's 2004 memo regarding a meeting with FDA explains that apremilast has a chiral center that is not acidic, and thus not racemizable like the chiral center found in thalidomide. DFF ¶ 1123-1138. FDA was satisfied with Celgene's descriptions distinguishing the structural characteristics of apremilast from thalidomide. *Id.*

278. By the time of the '358 patent, thalidomide analogs were being studied as potential new drugs. A POSA would have been interested in developing thalidomide analogs that lack an acidic hydrogen on the chiral carbon. DFF ¶ 1123-1138. Thalidomide was known as a racemic mixture and it was suggested to separate the enantiomers in order to avoid the side effects seen with the racemic mixture. *Id.*

279. The Court concludes that like other secondary considerations, the alleged skepticism is insufficient to support the non-obviousness of the asserted claims of the '638 and '536 patents.

D. There Is No Evidence Of Failures Of Others That Supports The Non-Obviousness Of The Asserted Claims Of The '638 And The '536 Patents.

280. In conducting a failure of others analysis, the relevant problem is solely that which the patent-in-suit purports to solve. *See Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d

1569, 1578 (Fed. Cir. 1991) ("[n]onobviousness is suggested by the failure of others to find a solution to the problem which the patent[s] in question purport[ ] to solve.") (citation omitted); *Oscar Mayer Foods Corp. v. ConAgra, Inc.,* 45 F.3d 443, at *4 (Fed. Cir. 1994) ("[T]he failure of others is probative only if they sought to overcome the problem the applicant claims to have solved.").

281. Generally, the cause of the failures must be attributable, in at least some degree, to the absence of the claimed aspects of the invention in the attempt for this consideration to have relevance to obviousness. *See Cubist Pharm., Inc. v. Hospira, Inc.,* 805 F.3d 1112, 1126 (Fed. Cir. 2015); *see also DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1371-72 (Fed. Cir. 2006) (holding that failed attempt was not evidence of secondary consideration of obviousness when failure was due to cost and not technical difficulty).

282. Like other secondary considerations, failure of others may be insufficient to rebut a finding of obviousness. *See Am. Sterilizer Co. v. Sybron Corp.,* 614 F.2d 890, 893 (3d Cir. 1980).

283. The Court finds Amgen has failed to establish the failure of others to support the non-obviousness of the asserted claims of the '638 and the '536 patents.

284. Dr. Knowles testified that apremilast "succeeded where many other PDE4 inhibitors had failed." DFF ¶ 1065.

285. However, Dr. Knowles never provided a clear definition of what would and would not constitute a failure of others and thus never established a legally cognizable secondary consideration. DFF ¶¶ 1065, 1066. Regardless, neither roflumilast nor any compound that reached clinical testing in humans could be considered a failure in the world of patents. DFF ¶¶ 1069-1073, 1088-1092.

1. The PDE4 Inhibitor Roflumilast Is Not A Failure.

286. The Court concludes that the PDE4 inhibitor roflumilast should not be considered a failure. DFF ¶¶ 1069-1073.

2. None Of The Compounds Dr. Knowles Discussed As Being Discontinued Were Apremilast, Let Alone Stereomerically Pure Apremilast And Dr. Knowles Was Unable To Provide The Reasons Why Many Of The Compounds He Discussed Were Discontinued.

287. None of the compounds Dr. Knowles discussed as being discontinued were apremilast, let alone stereomerically pure apremilast and Dr. Knowles was unable to provide the reasons why many of the compounds he discussed were discontinued. *See, e.g.*, *Acorda*, 2017 WL 1199767, at *39 (the cause of the failures must be attributable, in at least some degree, to the absence of the claimed aspects of the invention in the attempt for this consideration to have relevance to obviousness). DFF ¶¶ 1074-1083.

3. Drug Development Programs May Be Discontinued Due To Reasons Other Than Shortcomings In A Drug Candidate's Properties.

288. The decision to discontinue development of other drug candidates, including whether to move forward with seeking FDA approval involves complex, business-driven considerations that may not have been related to some sort of shortcoming with the drug candidate that would have prevented eventual FDA approval. *See DyStar*, 464 F.3d at 1371-72 (alleged failures of others that are based on economic decisions, and not with documented difficulties in implementing the technology, generally do not provide a valid secondary consideration of non-obviousness). DFF ¶¶ 1084-1087.

4. Many PDE4 Inhibitors Had Entered Clinical Trials In Humans As Of The Priority Date.

289. Dr. Knowles also implied that a failure would be found if a PDE4 inhibitor identified in step one of his drug development cascade failed to reach clinical studies in humans.

If the foregoing was the standard to be used in determining whether a compound was a failure, then many PDE4 inhibitors should not be found to be failures given that other compounds entered clinical studies in humans as of the priority date. DFF ¶¶ 1088-1092.

290. For the foregoing reasons, the Court concludes that Amgen (and Dr. Knowles) have failed to present persuasive evidence of any failures of others. DFF ¶¶ 1065-1092.

E. Amgen Presented No Evidence Of A Long-Felt, Unmet Need That Supports The Non-Obviousness Of The Asserted Claims Of The '638 And The '536 Patents.

291. The Court finds that Amgen failed to establish two separate long-felt unmet needs. The first relates to an ambiguous, purported need for an effective PDE4 inhibitor for use in humans, an argument propounded by Amgen's expert Dr. Knowles in relation to the '536 and '638 patents. The second was a need for a treatment for moderate plaque psoriasis that was safer than what existed prior and that lacked the potential barriers to adherence seen with other treatment options, as propounded by Amgen's dermatology expert, Dr. Alexis. DFF ¶¶ 1200, 1203-1204.

292. "[T]he patentee must point to an articulated and identified problem and evidence of efforts to solve the problem that were, before the invention, unsuccessful." *Apple Inc. v. Samsung Elecs. Co.,* 816 F.3d 788, 804-05 (Fed. Cir. 2016), *vacated in part on other grounds on reh'g en banc,* 839 F.3d 1034 (Fed. Cir. 2016); *see also Texas Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

293. "Evidence of a long-felt need is only probative of nonobviousness . . . when both a demand existed for the patented invention, and others tried but failed to satisfy that demand." *Copaxone*, 2017 WL 401943, at *23 (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.,* 676 F.3d 1063, 1083 (Fed. Cir. 2012)).

294. A long-felt but unmet need must be "sufficiently connected with the novel elements of the asserted claims." *Merck & Cie v. Gnosis S.P.A.,* 808 F.3d 829, 838 (Fed. Cir. 2015). And even if the patentee introduces evidence of a long-felt need ostensibly tied to the patent claims, where the differences between the prior art and the claimed invention are minimal, "it cannot be said that any long-felt need was unsolved." *Geo. M. Martin Co. v. All. Mach. Sys. Int'l LLC,* 618 F.3d 1294, 1304 (Fed. Cir. 2010).

295. "If prior art products were effective for the purpose of the claimed invention, there is no long-felt need." *AstraZeneca LP v. Breath Ltd.*, 88 F. Supp. 3d 326, 387 (D.N.J. 2015); *see also B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1583 (Fed. Cir. 1996) (discounting long-felt need because invention "was similar to the teachings" of prior art). "Evidence of the long-felt need factor must squarely address the need satisfied by ***the asserted claims themselves***." *AstraZeneca*, 88 F. Supp. 3d at 387.

296. Like other secondary considerations, long-felt need may be insufficient to rebut a finding of obviousness. *Graham v. John Deere Co. of Kansas City,* 383 U.S. 1, 36 (1966) (long-felt need did not overcome invention that was clearly obvious in view of prior art).

297. Amgen's experts did not present any evidence that there was a long-felt, unmet need for stereomerically pure apremilast, or pharmaceutical compositions thereof, in comparison to what was known in the prior art, including apremilast present in the racemic mixture of Example 12 of the '358 patent. DFF ¶¶ 1049-1053. Amgen and its experts did not present evidence of any need that was both long-felt and unmet, regardless of whether the "need" identified would meet the legal requirements for being a secondary consideration. *See In re Kahn*, 441 F.3d at 990-91 (establishing long-felt, unmet need "requires that the applicant submit actual evidence of long-felt need, as opposed to argument.").

1. There Was No Long-Felt Need For An Effective PDE4 Inhibitor.

298. After nine days of trial, the unmet "need" Dr. Knowles contends existed in the prior art before the '638 patent priority date still remains ambiguous. DFF ¶¶ 1049-1054. It appears from Dr. Knowles testimony that the "need" he articulated was for an effective PDE4 inhibitor suitable for human use in a pharmaceutical composition that minimized side effects. DFF ¶ 1049. That "need," however, had already been met by roflumilast, which the experts agree was an oral pharmaceutical composition comprising a PDE4 inhibitor that presented a safety and efficacy profile sufficient for FDA approval. DFF ¶¶ 1055-1059. Dr. Knowles' testimony on this issue was unclear as to at what point any drug might have met his "need"—whether it would have occurred when a compound first was identified as having potential pharmaceutical utility or it would have occurred only upon FDA approval many years later. DFF ¶¶ 1049-1054. If the former, many compounds met that "need" when they passed one or more steps in Dr. Knowles testing cascade. DFF ¶¶ 1060-1063. If the latter, the parties agreed that roflumilast received FDA approval before apremilast. DFF ¶¶ 1055-1059.

299. The oral PDE4 inhibitor roflumilast obtained FDA approval in 2011, prior to apremilast obtaining FDA approval. Roflumilast is a PDE4 inhibitor suitable for use as a pharmaceutical composition. Roflumilast was effective and minimized side effects and was approved by the FDA. The oral PDE4 inhibitor roflumilast obtained FDA approval in 2011, prior to Otezla® (apremilast) obtaining FDA approval. Therefore, roflumilast would have met Dr. Knowles's alleged need. DFF ¶¶ 1055-1059.

300. At other times, Dr. Knowles referenced his arguments about the therapeutic index as part of his long-felt, unmet need analysis. DFF ¶ 1054. Dr. Knowles did not explain how his analysis of apremilast's therapeutic index with respect to emesis met a "need" identified in the prior art to a person of skill in the art and why. *Id.*

301. To the extent Amgen contends that apremilast met Dr. Knowles's alleged need due to the compound apremilast having "suitable potency, safety, drug-like properties, and a sufficiently high therapeutic index to make it suitable for a pharmaceutical composition to treat humans", as of the priority date, there were PDE4 inhibitors that had demonstrated suitable drug-like properties and could thus have met the alleged need. DFF ¶¶ 1060-1064. The Court finds Amgen and Dr. Knowles did not put forth persuasive evidence of a long-felt unmet need. DFF ¶¶ 1049-1064.

2. There Is No Long-Felt Unmet Need For A Treatment For Moderate Plaque Psoriasis That Was Safer Than What Existed Prior And That Lacked The Potential Barriers To Adherence That Was Met By Apremilast.

302. To the extent that Amgen is arguing that there was a long-felt, but unmet need for apremilast as a treatment for psoriasis, that argument ignores Otezla®'s role in the marketplace as well as the prior art treatments that were available. According to Dr. Alexis, apremilast satisfied a long-felt and unmet need for a treatment for moderate plaque psoriasis that was safer than what existed prior and that lacked the potential barriers to adherence seen with other treatment options. DFF ¶1200. The Court finds Amgen's proffered evidence did not establish the existence of a long-felt need let alone a need that apremilast filled for several reasons.

303. ***First,*** there are ***no limitations*** in the asserted claim of the '536 patent directed to safety or the elimination of potential barriers to adherence of other treatments. DFF ¶¶ 1201, 1203. The '536 patent simply claims a method of treating psoriasis by administering stereomerically-pure apremilast over a broad dosing range. DFF ¶ 1201. Further, nothing in the specifications of the '536 patent describes the characteristics of a "safer" treatment or "lack of potential barriers to adherence of other treatment options" as being allegedly novel aspect of the claimed invention of the '536 patent over the prior art. DFF ¶ 1205. In addition, the '536

patent's method of treatment claims are not limited to moderate plaque psoriasis, but broadly claim a "method of treating psoriasis." DFF ¶ 1201. Thus, Amgen's alleged evidence has no relation to, and is not commensurate in scope with, the invention claimed in the asserted claim of the '536 patent. *AstraZeneca*, 88 F. Supp. 3d at 388-89.

304. ***Second***, apremilast did not satisfy any long-felt need in the treatment of patients suffering from psoriasis that was not met by other existing, prior art treatments in March 2002. Before the filing date of the '536 patent and long before Otezla® was approved by FDA, there were several existing therapies that were effective and used for treating psoriasis, including moderate plaque psoriasis, all of which were FDA approved. DFF ¶¶ 1207, 1210-1215. For example, methotrexate was an oral treatment known to be an effective therapy for patients with moderate to severe plaque psoriasis, has been in use since the 1950s, and "remains the ***most commonly used*** treatment for psoriasis." DFF ¶ 1211 (emphasis added). Indeed, both dermatology experts, Drs. Gilmore and Alexis, still prescribe methotrexate in their practices today. *Id*

305. Biologics were another class of drugs available in the prior art and effective for systemically treating psoriasis before apremilast. DFF ¶¶ 1211-1217. Biologics were not only more effective in treating psoriasis that other prior art therapies, but they were also associated with fewer side effects. *Id.*

306. Further evidence that biologics were the transformative therapy and not apremilast is that even after Otezla® was approved, there was continued interest in further developing biologic drugs—with studies showing that with these newer biologics showed complete clearance of patients' skin. DFF ¶¶ 1218-1220. Thus, even if there was a long-felt but unmet need for a psoriasis treatment before apremilast, it was met by the use of conventional,

oral systemic therapies, such as methotrexate, and the early biologic drugs. DFF ¶ 1220. To the extent such need still existed after apremilast, it was met by the newer generation of biologic drugs, which have shown the ability to achieve 100% clearance of psoriatic plaques and lesions. DFF ¶¶ 1218-1220. The Court finds Amgen's arguments, unsupported by data or documents, that patients would choose to use apremilast over other established treatments for such reasons is unpersuasove and contradicted by the scientific literature and internal Celgene documents. DFF ¶¶ 1221-1235.

307. ***Third***, even if a long-felt unmet need existed, apremilast did not satisfy it. There is currently no cure for psoriasis, and as such, the goal of treatment is to decrease the severity and extent of clinical symptoms and increase the quality of life. DFF ¶ 1221. Apremilast is not more effective than methotrexate and is significantly less effective than biologics. DFF ¶¶ 1222-1227. Apremilast's safety profile is no more favorable than any other therapy available for moderate to severe psoriasis. DFF ¶¶ 1228-1235. Indeed, apremilast is associated with significant gastrointestinal-related side effects that negatively impact patients' already poor quality of life and an increased incidence of depression. DFF ¶¶ 1228-1233. Even using the titration scheduled in the Otezla® label, 40-50% of patients discontinue treatment because they cannot tolerate the gastrointestinal-related side effects. DFF ¶ 1230.

308. That apremilast does not have a black box warning or require lab monitoring does not satisfy a long-felt but unmet need for a safer drug or imply that Otezla® is safer than methotrexate or biologics. DFF ¶ 1234. Methotrexate, biologics, and apremilast all have warnings and precautions in their labels that physicians are trained to assess and consider with each patient to determine the best course of treatment. DFF ¶¶ 1234-1235. At best, apremilast is

simply one more drug in the armamentarium of physicians, and one that is limited in use by its debilitating side effect profile and mediocre efficacy. *Id.*

309. ***Fourth***, Amgen has failed to demonstrate a nexus between the allegedly novel features of the '536 patent and any alleged long-felt, unmet need. To the extent that there are any advantages associated with apremilast, they result from the compound itself, which Celgene disclosed in the prior art '358 patent. *See, e.g.*, DFF ¶¶ 809-820. Amgen thus cannot "establish a nexus between the evidence and the *claimed invention*"—a "fundamental requirement that must be met before secondary considerations can carry the day." *In re Huai-Hung Kao*, 639 F.3d at 1068. At best, Amgen's objective evidence "results from something other than what is both claimed and novel in the claim, [so] there is no nexus to the merits of the claimed invention." *Id.*

310. ***Finally***, even if a person of skill in the art would have found an unmet need for the type of treatment claimed in the '536 patent, that person of skill in the art would have faced a legal bar—the '358 patent—to developing that treatment, even if it were obvious. The fact that others did not practice what is claimed in the '536 patents before 2002 sheds no light on whether the claimed treatment was obvious, because others were blocked under the patent laws from using this treatment. Thus, this secondary consideration of nonobviousness has little bearing to this case in the face of the '358 blocking patent. *Acorda*, 903 F.3d at 1339.

F. Apremilast Does Not Demonstrate "Clinical Success."

311. With nothing to support the argument other than anecdotal evidence from their dermatology expert, Dr. Alexis, Amgen asserts that Otezla® has attained success in the clinic. The Court finds an initial matter that clinical success is not a recognized secondary consideration of nonobviousness. *See KSR,* 550 U.S. at 406 (identifying several recognized secondary considerations with no mention of clinical success); *Power Integ., Inc. v. Fairchild*

Semiconductor Int'l, Inc., 711 F.3d 1348, 1368 (Fed. Cir. 2013) (same). There is no case law that defines what requirements are needed to prove "clinical success" nor can Amgen point to any.

312. Amgen appears to consider "clinical success" a hybrid of long-felt unmet need and commercial success. In its pretrial brief, Amgen's only mention of "clinical" success is in the context of arguing that "Otezla's clinical success in treating plaque psoriasis has translated into commercial success." Amgen's Pre-trial Br. At 46. Regardless of its status as a secondary consideration, the Court concludes Amgen has failed to establish that apremilast (and Otezla®) was a clinical success and its argument is legally flawed for the same reasons as the long-felt unmet need arguments.

313. Dr. Alexis offered the conclusion that Otezla is a clinical success. DFF ¶ 1236. He further testified that the "clinical success" was due to Otezla's "safety profile," the "lack of lab monitoring," and the "oral route of administration." *Id.* Dr. Alexis does not cite to a ***single*** document, piece of scientific literature, or anything other than what appears to be his personal opinion and uncorroborated "opinions" of unidentified colleagues to support this opinion. *Id*. The Court is not persuaded by the opinion of one physician, who did not consider the negative tolerability and mediocre efficacy data of Otezla® during his direct examination, as establishing any objective indicia of nonobviousness, let alone one that is not legally recognized.

314. Even assuming that "clinical success" is a valid secondary consideration of nonobviousness, Amgen's argument is outweighed by the credible and evidence-based testimony of Dr. Gilmore and supporting documentation in which it is clear that Otezla® does not have clinical success due to the inventions of the asserted claims for at least four reasons: (1) biologics are significantly more efficacious and require less frequent dosing; (2) methotrexate, another orally dosed medication, is still widely prescribed, has similar efficacy to Otezla®, is less

expensive, and requires less frequent dosing; (3) Otezla® is accompanied by incapacitating gastrointestinal side-effects that often lead to discontinuation; and (4) the marketing of Otezla® influences prescribing practices as opposed to any positive attributes of the drug. DFF ¶ 1236-1249.

G. Apremilast Does Not Demonstrate Commercial Success.

315. The Court finds Amgen did not overcome Defendants' showing of *prima facie* obviousness based on any argument that Otezla is allegedly a commercial success. A patentee offering evidence of commercial success to support a nonobviousness determination bears the burden of proving two things. First, that there was commercial success. *Merck & Co., Inc. v. Teva Pharms. USA, Inc*., 395 F.3d 1364, 1376 (Fed. Cir. 2005). Second, that there is some causal relation, or nexus, between any such success and the patented attributes of the product. *Id.* Commercial success is relevant "only if there is proof that the sales were a direct result of the unique characteristics of the claimed invention—as opposed to other economic and commercial factors unrelated to the quality of the patented subject matter." *In re Huang*, 100 F.3d 135, 140 (Fed Cir. 1996). Moreover, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Galderma Labs. L.P. v. Tolmar, Inc*., 737 F.3d 731, 740 (Fed. Cir. 2013) (quoting *Ormco Corp. v. Align Tech., Inc*., 563 f.3d 1299, 1311-12 (Fed. Cir. 2006)). The Court concludes Amgen did not demonstrate that Otezla's marketplace performance meets the second "nexus" prong, for several reasons. DFF ¶¶ 1270-71.

316. *First*, any evidence of Otezla's marketplace performance is not relevant to the obviousness inquiry because the '358 patent was a blocking patent that precluded others from bringing a product like Otezla to the market. DFF ¶¶ 1251-69. Commercial success is potentially relevant to the obviousness analysis in general because the law presumes an idea would have been brought to market sooner, in response to market forces, had it been obvious to

persons skilled in the art. *Merck*, 395 F.3d at 1376. But where, as here, the idea could not be brought to market by others because of a blocking patent like the '358 patent, "[t]hat rationale has no force." *Id.* Where "market entry by others was precluded" because of other patents, evidence of commercial success is of negligible value. *Id.* at 1377*; see also Galderma Labs.,* 737 F.3d at 740 (according evidence of commercial success "minimal probative value" where market entry was blocked by earlier-expiring compound patent).

317. Here, the '358 patent undisputedly covered the use of all products that contain the compound apremilast. DFF ¶¶ 1254; 1272. As such, others could not have entered the market for apremilast formulations until the expiration of the '358 patent in 2018. DFF ¶¶ 1251, 1256, 1260. Thus, even if Amgen could show that commercial success is caused by the alleged inventions of the '638 and '536 patents (and it cannot), that showing still could not overcome the strong *prima facie* case presented by Defendants because the '358 patent—not anything inventive about the '638 and '536 patents—was responsible for keeping others from making a product like Otezla before Amgen. DFF ¶¶ 1254; 1272.

318. The disincentives for others to develop the invention claimed in the '638 and '536 patents due to the blocking nature of the '358 patent are further confirmed by the factors set out in *Acorda*, 903 F.3d at 1338 (the "Ampyra factors"); *see also* DFF ¶ 1257. In that case the Federal Circuit analyzed several considerations in determining whether a blocking patent defeats evidence of commercial success. *Acorda,* 903 F.3d at 1338. One consideration is the likelihood of a successful challenge to the blocking patent. *Id.* There were no challenges to the validity of the '358 patent prior to its expiration in 2018. DFF ¶ 1258. The Court also considers the costs associated with pursuing the project in an environment with blocking patents. *Acorda,* 903 F.3d at 1338. Mr. Hofmann determined competitors would lack economic incentive to incur the costs

to potentially develop the technology of the '638 and '536 patents because of the significant risk they would not be able to subsequently commercialize a product that practices those patents until the '358 patent expires in 2018. DFF ¶¶ 1259-63. Another consideration is the nature of improvements that might arise from the project, and whether such improvements will be entirely covered by the blocking patent. *Acorda*, 903 F.3d at 1338. Here, as previously discussed, any practice of the claims of the '638 and '536 patents is entirely covered by the '358 patent because the '638 and '536 patents are dependent on the use of the apremilast compound itself, which is covered by the '358 patent. DFF ¶¶ 1254; 1259-63, 1272. Additional considerations include the risk of losing the invention race, and the risk that the patent owner would refuse to license. *Acorda*, 903 F.3d at 1338. Others in the industry understood that Amgen had won the invention race, and the focus of Celgene's licensing efforts on a development partner would have further disincentivized other industry participants from pursuing the inventions claimed in the '638 and '536 patents. DFF ¶¶ 1261-69

319. Second, Amgen has not established a nexus between the commercial success and the claimed inventions. *In re Huai-Hung Kao*, 639 F.3d at 1068; *J.T. Eaton & Co. v. Atlantic Paste & Gluc Co*., 106 F.3d 1563, 1571 (Fed. Cir. 1997) ("the asserted commercial success of the product must be due to the merits of the claimed invention beyond what was readily available in the prior art."). "[I]f the commercial success is due to an unclaimed feature … commercial success is irrelevant." *Ormco Corp.*, 463 F.3d at 1312. Where there is no evidence that the commercial success of a pharmaceutical drug is due to anything besides its prior art active ingredient, there is no nexus. *See Aventis*, 743 F. Supp. 2d at 348.

320. Here, Otzela®'s marketplace performance is not due to the claimed formulations of the asserted patents. Instead, Amgen's own expert contends that Otezla®'s commercial

success is attributable to the apremilast compound of the '358 patent, which is prior art. DFF ¶¶ 1272 The sales drivers that Dr. Vellturo identified as driving its marketplace performance—it's PDE4 inhibiting mechanism of action, the safety and efficacy, the non-injectable form and lack of need for laboratory monitoring—are all attributable to the apremilast compound disclosed in the '358 patent and not to what is allegedly new in the claims of the '638 and '536 patents. *Id*.

321. Third, Otezla's marketplace performance is also attributable to a variety of reasons that have nothing to do with the claims of the '638 and '536 patents. Indeed, the significant amount of promotional expenditures incurred by Amgen in connection with Otezla "obscur[es] any nexus that might have existed between the merits of the product and its commercial success." *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1370 (Fed. Cir. 2003) (citation omitted); *see also Pentec, Inc. v. Graphic Controls Corp*., 776 F.2d 309, 316 (Fed. Cir. 1985) (concluding that patentee failed to show the required nexus where commercial success may have been due to "'other economic and commercial factors unrelated to the technical quality of the patented subject matter,'" including an extensive advertising campaign (citation omitted)). Where the alleged success could just as easily be attributed to marketing power or capabilities, even if it is "found that the claimed invention was a 'commercial success,' this evidence does not convince us that the invention was not obvious." *Richardson-Vicks Inc. v. Upjohn Co*., 122 F.3d 1476, 1484 (Fed. Cir. 1997) (recognizing that the advantages of the active ingredient "were well known by doctors and patients alike").

322. [redacted]

323. Therefore, the Court concludes the commercial success of Otezla® is of no relevance to an obviousness analysis of the asserted patents.

IV. The Asserted Claims Of The '101 Patent Are Invalid.

324. The Court concludes claims 1 and 15 of the '101 patent are invalid as obvious over the prior art as of March 27, 2008. As explained in more detail below, the Court finds Amgen did not meet its burden to demonstrate that claims 1 and 15 of the '101 patent are entitled to a March 20, 2002 priority date. Further, Amgen did not present any evidence to rebut Defendants' clear and convincing evidence of obviousness as of March 27, 2008.

A. The Priority Date For The '101 Patent Is March 27, 2008.

1. Amgen Bears The Burden Of Showing The '101 Patent Is Entitled To A Priority Date Earlier Than March 27, 2008.

325. It is well-settled that "[p]atent claims are not entitled to an earlier priority date merely because the patentee claims priority. Rather, for a patent's claims to be entitled to an earlier priority date, the patentee must *demonstrate* that the claims meet the requirements of 35 U.S.C. § 120." *Nat. Alternatives Int'l, Inc. v. Iancu*, 904 F.3d 1375, 1380 (Fed. Cir. 2018) (citing *In re NTP, Inc.*, 654 F.3d 1268, 1276 (Fed. Cir. 2011)) (emphasis in the original) (internal quotation omitted). Thus, claims in a patent or patent application are not entitled to an earlier priority date under § 120 "at least until the patent owner *proves* entitlement to the PTO, the Board, or a federal court." *Id.* (emphasis in the original) (internal quotation and citation omitted).

326. Where, as here, neither the Patent Office nor the Patent Trial and Appeal Board has previously considered priority, "there is simply no reason to presume that claims in a [continuation-in-part] application are entitled to the effective filing date of an earlier filed application," so the district court may place the burden on the patent owner to "come forward

with evidence to prove entitlement to claim priority to an earlier filing date" *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1305–06 (Fed. Cir. 2008); *see also Geospatial Technology Associates, LLC v. United States*, 2021 WL 2325007, *15 (Fed. Cl. Apr. 08, 2021).

327. It is undisputed that the '101 patent was filed on March 27, 2008, as a continuation-in-part application ("CIP") of earlier-filed, related applications. DFF ¶¶ 64-68, 1404-05, 1407. Thus, the Court finds it is Amgen's burden to show that claims 1 and 15 of the '101 patent are entitled to a priority date earlier than March 27, 2008. *See Nat. Alternatives Int'l*, 904 F.3d at 1380; *PowerOasis*, 522 F.3d at 1305–06.

2. Amgen Has Failed To Show Claims 1 and 15 Of The '101 Patent Are Entitled To A Priority Date Earlier Than March 27, 2008.

328. Amgen asserts claims 1 and 15 of the '101 patent are entitled to a priority date of March 20, 2002, when the earliest filed application related to the '101 patent, U.S. Provisional Application No. 60/366,515 ("the '515 application"), was filed. DFF ¶¶ 65, 1417. Claim 1 of the '101 patent is directed to the crystalline Form B of enantiomerically pure apremilast, with an X-ray powder diffraction pattern comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ. *Id.* ¶ 72. Claim 15 of the '101 patent is directed to a solid pharmaceutical composition comprising the crystalline Form B of enantiomerically pure apremilast recited in claim 1. *Id.* ¶ 73. Thus, to meet its burden, Amgen must demonstrate that the '515 application provides written description support for the crystalline Form B of enantiomerically pure apremilast recited in claims 1 and 15. *See, e.g.,* 35 U.S.C. § 120. The Court finds Amgen did not meet this burden.

a. The Legal Standard For Showing Entitlement To Priority Date Before The '101 Patent's Filing Date.

329. Under 35 U.S.C. § 120, "a claim in a later application receives the benefit of the filing date of an earlier application so long as the disclosure in the earlier application meets the requirements of 35 U.S.C. § 112, ¶ 1, including the written description requirement, with respect

to that claim." *Cordance Corp. v. Amazon.com, Inc.*, 658 F.3d 1330, 1334 (Fed. Cir. 2011) (citing *Tech. Licensing Corp. v. Videotek, Inc*., 545 F.3d 1316, 1326 (Fed. Cir. 2008)); *see also In re Chu*, 66 F.3d 292, 297 (Fed. Cir. 1995) ("It is elementary patent law that a patent application is entitled to the benefit of the filing date of an earlier filed application only if the disclosure of the earlier application provides support for the claims of the later application, as required by 35 U.S.C. § 112.").

330. 35 U.S.C. § 112, ¶ 1 states that the patent's specification or disclosure "shall contain a written description of the invention." *See Ariad Pharms., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1344 (Fed. Cir. 2010) (en banc). The "requirement to describe one's invention is basic to patent law. Every patent must describe an invention. It is part of the *quid pro quo* of a patent; one describes an invention, and, if the law's other requirements are met, one obtains a patent." *Id.* at 1345.

331. "To satisfy the written description requirement, the disclosure of the earlier filed application must describe the later claimed invention 'in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought.' " *Tech. Licensing Corp. v. Videotek, Inc*., 545 F.3d 1316, 1331 (Fed. Cir. 2008) (quoting *Lockwood v. Am. Airlines, Inc*., 107 F.3d 1565, 1572 (Fed. Cir. 1997)). "While the earlier application need not describe the claimed subject matter in precisely the same terms as found in the claims at issue, the prior application must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, [the inventor] was in possession of the invention." *Id.* at 1331–32.

332. The Federal Circuit has explained that "the hallmark of written description is disclosure." *Ariad*, 598 F.3d at 1351. Thus, the written description test "requires an objective

inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed." *Id.* In other words, to satisfy the written description, "one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims." *Purdue Pharma L.P. v. Faulding Inc*., 230 F.3d 1320, 1323 (Fed. Cir. 2000).

333. The written description requirement is met when the disclosure "allow[s] one skilled in the art to visualize or recognize the identity of the subject matter purportedly described." *Enzo Biochem, Inc. v. Gen–Probe Inc.,* 323 F.3d 956, 968 (Fed. Cir. 2002). Thus, "the written description requirement is satisfied by the patentee's disclosure of such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." *Id.* at 969.

334. Further, the Federal Circuit has "repeatedly stated that actual possession or reduction to practice outside of the specification is not enough. Rather, [] it is the specification itself that must demonstrate possession." *Ariad*, 598 F.3d at 1352. *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1309 (Fed. Cir. 2015) (finding that the district court erred by relying on "the undisclosed clinical protocol to support its written description determination," explaining that "[t]he written description requirement requires possession *as shown in the specification*") (emphasis in the original).

335. It is also well-settled that "a description that merely renders the invention obvious does not satisfy the [written description] requirement." *Ariad*, 598 F.3d at 1352; *see also Lucent Technologies, Inc. v. Gateway, Inc*., 543 F.3d 710, 719 (Fed. Cir. 2008) ("the court correctly

recognized that a demonstration of obviousness is not sufficient to show possession."); *Lockwood v. Am. Airlines*, 107 F.3d 1565, 1571–72 (Fed. Cir. 1997).

336. The Federal Circuit has also long recognized that "one cannot describe what one has not conceived." *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993) (affirming finding that the priority application failed to provide an adequate written description for claims directed to DNA that coded a specific protein because the priority application did not describe specific DNA that could code the protein and only provided a generic reference that workable DNA could be obtained by reverse transcription); *see also Tech. Licensing Corp. v. Videotek, Inc*., 545 F.3d 1316, 1333–34, (Fed. Cir. 2008) (holding that a parent application did not support the claim added in a CIP application).

337. Only "on rare and special occasions, [the Federal Circuit has] stated that commonplace properties of a claimed invention may be deemed 'inherent' to the invention." *Hitzeman v. Rutter*, 243 F.3d 1345, 1354 (Fed. Cir. 2001). "Inherent" properties, "are the rare exceptions to the rule that a party must show possession of every feature recited in the [claim] and that every limitation of the claim must have been known to the inventor at the time of the alleged conception." *Id.* at 1354–55. Further, "[i]n the context of priority determinations, the allegedly inherent limitation cannot be material to the patentability of the invention." *Id.* at 1355.

338. The written description requirement may be satisfied without an explicit disclosure only under a narrow set of circumstances. However, it is long established that the alleged inherent property *must necessarily occur*—showing only that the alleged inherent function, characteristic, or property *might* occur is insufficient. *See, e.g., Hansgirg v. Kemmer*, 102 F.2d 212 (C.C.P.A. 1939) (no inherency where the performance of the alleged inherent

function was only a possibility, not an *absolute* occurrence); *Glaxo Inc. v. Novopharm Ltd*., 52 F.3d 1043, 1047 (Fed. Cir. 1995) (no inherent disclosure where it was shown that the allegedly inherent crystalline form was not produced every time when following the teachings of the reference); *Rexnord Industries, LLC v. Kappos*, 705 F.3d 1347, 1354–55 (Fed. Cir. 2013) (inherency was not found due to lack of precision and specificity in the disclosure); *Endo Pharms. Solutions Inc. v. Custopharm, Inc*., 234 F. Supp. 3d 587, 600 (D. Del. 2017), aff'd, 894 F.3d 1374, 1381–83 (Fed. Cir. 2018) (finding the presence of benzyl benzoate or its ratio with castor oil was not inherent in the disclosure because of failure to establish that the disclosure barred the possibility of an alternative vehicle being used); *In re Armodafinil Patent Litigation*, 939 F. Supp. 2d 456, 470 (D. Del. 2013) (finding the disclosure at issue was not shown to "necessarily and inevitably" result in armodafinil crystalline Form I, because the evidence presented at trial showed that the disclosure at issue could yield different forms, mixtures of forms, and unknown impurities, depending on the variables selected in conducting the disclosed procedure).

b. Claims 1 And 15 Are Not Entitled To A Priority Date Before March 27, 2008 Because The Information Supporting The Claimed Apremilast Crystalline Form B Was Added To The '101 Patent Specification For The First Time On March 27, 2008.

339. The Federal Circuit has long recognized that "[s]ubject matter that arises for the first time in the CIP application does not receive the benefit of the filing date of the parent application." *Augustine Med., Inc. v. Gaymar Indus., Inc*., 181 F.3d 1291, 1302 (Fed. Cir. 1999); *see also Go Med. Indus. Pty., Ltd. v. Inmed Corp*., 471 F.3d 1264, 1270 (Fed. Cir. 2006) ("New subject matter does not receive the benefit of the earlier priority date."); *Paice LLC v. Ford Motor Co.*, 881 F.3d 894, 906 (Fed. Cir. 2018) ("The priority date for later-added patent claims

depends on when the claimed subject matter first appeared in the chain of patent applications from which the claims arose.").

340. The parties agreed that the '101 patent was filed on March 27, 2008, as a CIP of earlier-filed, related applications. DFF ¶¶ 64-68. The parties also agreed that for the first time on March 27, 2008, new information was added to the '101 patent describing solid forms of apremilast, and methods for preparing and characterizing solid forms of apremilast. DFF ¶¶ 67, 1404. The newly added information included information describing the preparation, identification, and characterization of the claimed apremilast crystalline Form B using characterization techniques XRPD, DSC, TGA, and DVS. *Id.* ¶ 1405. Based on the newly added information to the '101 patent specification a POSA, *id.* ¶¶ 1400-02, would have recognized that the named inventors of the '101 patent were in possession of the claimed apremilast crystalline Form B as of March 27, 2008, because a POSA could clearly and immediately discern the claimed limitations from the newly added description. DFF ¶¶ 1403-06; *Ariad*, 598 F.3d at 1352–53; *Tech. Licensing*, 545 F.3d at 1331–32; *Purdue Pharma*, 230 F.3d at 1323.

341. Celgene sought and obtained claims to apremilast crystalline Form B *only* after adding information describing the preparation and characterization of the claimed apremilast crystalline Form B to the '101 patent on March 27, 2008. DFF ¶¶ 1407-09. Further, Jean Xu, the inventor listed on the '101 patent who performed the polymorph screen on enantiomerically pure apremilast that led to the preparation and characterization of several apremilast solid forms, including the claimed apremilast crystalline Form B, was added as a named inventor to the '101 patent on March 27, 2008. DFF ¶¶ 63, 1412. Thus, the named inventors of the '101 patent filed a new CIP application, with newly added information and a newly added named inventor, to seek

and obtain claims directed to apremilast crystalline Form B. *Id.* ¶¶ 1407-09, 1412. The Court finds this shows that the named inventors of the '101 patent understood that the newly added information was required to provide written description support for patent claims covering apremilast crystalline Form B. *Ariad*, 598 F.3d at 1352–53; *Tech. Licensing*, 545 F.3d at 1331–32; *Purdue Pharma*, 230 F.3d at 1323.

342. Because the requisite disclosure describing the preparation and characterization of the claimed apremilast crystalline Form B was added "for the first time in the CIP application," the Court Concludes that apremilast crystalline Form B of claims 1 and 15 "does not receive the benefit of the filing date of the [earlier] parent application." *Augustine Med.*, 181 F.3d at 1302; *see also Go Med. Indus.*, 471 F.3d at 1270 ("New subject matter does not receive the benefit of the earlier priority date."); *Paice*, 881 F.3d at 906 ("The priority date for later-added patent claims depends on when the claimed subject matter first appeared in the chain of patent applications from which the claims arose.").

c. Amgen Has Failed to Show That The '515 Application Provides Written Description Support For the Claimed Apremilast Crystalline Form B.

343. Amgen relies solely on a partial sentence in Example 2 of the '515 application to support its asserted priority date of March 20, 2002. DFF ¶ 1417. As explained in more detail below, the Court finds neither Example 2, nor any other part of the '515 application, filed on March 20, 2002, includes any description, information, or data that would allow a POSA to immediately discern crystalline apremilast Form B claimed in claims 1 and 15 of the '101 patent, or to clearly conclude the named inventors of the '515 application actually invented, or were in possession of, crystalline apremilast Form B claimed in claims 1 and 15 of the '101 patent. *Enzo Biochem*, 323 F.3d at 968–69; *Purdue*, 230 F.3d at 1323; *Tech. Licensing*, 545 F.3d at 1331–32; *Ariad*, 598 F.3d at 1351 (explaining that "actual possession or reduction to practice outside of the

specification is not enough. Rather, [] it is the specification itself that must demonstrate possession.").

344. To be sure, and as explained in detail below in Section IV.B, the Court finds that Example 2 in combination with the knowledge of a POSA renders the claimed apremilast crystalline Form B obvious. However, "a description that merely renders the invention obvious does not satisfy the [written description] requirement." *Ariad*, 598 F.3d at 1352; *see also Lucent Techs*, 543 F.3d at 719 ("the court correctly recognized that a demonstration of obviousness is not sufficient to show possession."); *Lockwood*, 107 F.3d at 1571–72.

345. Thus, the Court finds Amgen did not meet its burden to show that the '515 application provides written description support for the claimed apremilast crystalline Form B. *See Cordance*, 658 F.3d at 1334 (affirming grant of JMOL that the claim at issue in a CIP application was not entitled to an earlier priority date where the earlier filed application did not support the claim filed in the CIP application); *In re Chu*, 66 F.3d at 297 (holding the claims at issue were not supported by "the Doyle patent disclosure," thus "Chu cannot obtain the benefit of the Doyle patent filing date for these claims and the Doyle patent was properly relied on as prior art.").

i. Example 2 Does Not Disclose An Apremilast Crystalline Form.

346. The parties agree that Example 2 of the '515 application does not explicitly disclose an apremilast *crystalline* form—it merely discloses an apremilast "solid." DFF ¶¶ 1411, 1418-1426. The parties also agree that a solid compound may exist in different solid forms, including crystalline and amorphous (i.e., non-crystalline) solids. DFF ¶¶ 1419, 1425, 1444. Thus, Amgen did not show that a POSA can visualize or recognize from Example 2 of the '515 application the particular form of the "solid" apremilast obtained at the end of step 4, or that the

named inventors of the '515 application invented, or were in possession of, a *crystalline* form of apremilast. In other words, Amgen did not show that a POSA reading Example 2 of the '515 application would "immediately discern" an apremilast *crystalline* form.

347. Example 2 of the '515 application does not disclose any other words, structures, figures, diagrams, formulas, or any other descriptive or analytical information about particular solid form of the "solid" obtained in Example 2. DFF ¶¶ 1418-26; *Enzo Biochem*, 323 F.3d at 969. The parties agree that Example 2 discloses a 4-step recipe for the chemical synthesis and purification of enantiomerically pure apremilast. DFF ¶¶ 1418-20. As Amgen's expert, Dr. Myerson testified, the concepts of crystallization and polymorphism are not related to enantiomers. DFF ¶ 1418.

348. While Example 2 describes the product obtained at the end of step 4 as a "solid" without any additional description, it describes another compound obtained in step 2 (an intermediate) as a "***crystalline*** solid." DFF ¶¶ 1421-22. The Court finds a POSA would understand from the Example 2 disclosure that the named inventors obtained a solid at the end of step 2 that, based on visual investigation, appeared to be crystalline and the named inventors of the '515 application explicitly described that observation in step 2 of Example 2. *Id*. ¶ 1421. In contrast, a POSA would understand from the Example 2 disclosure that the named inventors of the '515 application did not visually observe the solid obtained in the last step of apremilast synthesis to be a crystalline solid. *Id*. Nor did the named inventors of the '515 application provide any solid form data in Example 2 to further characterize and describe the apremilast solid obtained in the last step. DFF ¶¶ 1423-25. Critically, Amgen's expert, Dr. Myerson, did not rebut Prof. Steed's testimony as to how a POSA would understand these disclosures of Example 2 in its entirety.

349. The '515 application does not disclose any other words, structures, figures, diagrams, formulas, or any other descriptive or analytical information about the particular form of the "solid" obtained in Example 2 in any other part of the '515 application. DFF ¶¶ 1413-16.

350. The Federal Circuit has recognized that "one cannot describe what one has not conceived." *Fiers*, 984 F.2d at 1171; *see also Tech. Licensing*, 545 F.3d at 1333–34 (holding that a parent application did not support the claim added in a CIP application). In *Tech. Licensing*, the Federal Circuit rejected the argument that support was found in the parent application because two resistors shown in a drawing in the parent application had to operate the same as two resistors of a resistor network added to a CIP application. *Id.* The Federal Circuit explained that even if the resistors in the parent application functioned the same as the network in the CIP application, that did not show that at the time of the parent application the inventor *possessed the idea* of using the two resistors. *Id.*

351. Amgen has not presented any evidence that could show the named inventors of the '515 application had conceived of a *crystalline* form of apremilast by March 20, 2002, to be able to describe it in the '515 application. *Fiers*, 984 F.2d at 1171; *Tech. Licensing*, 545 F.3d at 1333–34. The only named inventors listed on the '515 application that the Court heard from were Dr. Peter Schafer and Dr. Muller. DFF ¶ 1430. Neither Dr. Schafer's testimony nor Dr. Muller's testimony did include any statement regarding apremilast solid forms. *Id*. Instead, the Court finds based on the disclosures in the '515 application, a POSA would understand that Example 2, or the '515 application, were not directed to the solid forms of apremilast—rather, it was directed to preparation and methods of using enantiomerically pure apremilast. *Id.* ¶¶ 1413-16, 1423-26.

352. Further, Amgen's expert admitted that "you can only know [a crystalline form] exists after you've discovered it and characterized it." DFF ¶ 1426. A POSA understands that a crystalline form is identified by its unique set of characterization data. *Id.* Because neither Example 2 nor the '515 application disclose any descriptive or analytical data regarding the solid form of the "solid" obtained at the last step of apremilast synthesis, *id.* ¶¶ 1413-16, 1421, 1423-25, they cannot show that the named inventors of the '515 application had conceived of a *crystalline* form of apremilast by March 20, 2002, to be able to describe it in the '515 application.

353. The evidence presented at trial showed that Ms. Jean Xu, who is a named inventor on the '101 patent but not on the '515 application, was asked to perform a polymorph screen on apremilast in August 2003, more than sixteen months after the '515 application was filed. DFF ¶ 1412. Ms. Xu then identified and characterized seven different crystalline forms of apremilast, including the claimed apremilast crystalline Form B, the preparation information and characterization data for which were added to the '101 patent on March 27, 2008. *Id.* ¶¶ 1404-05, 1412. Ms. Xu prepared the apremilast polymorph screening report dated April 2, 2004, which describes her identifying and characterizing seven apremilast crystalline forms. *Id.* ¶ 1422. In this report, Ms. Xu described apremilast crystalline Form B as appearing as "a white, flaky ***crystalline*** solid." *Id.* Thus, when Ms. Xu prepared an apremilast crystalline form, she knew how to visually describe it as such. *Id.* Notably, such characterization is completely absent from the step 4 disclosure of Example 2 of the '515 application that Amgen relies on. *Compare id. with* DFF ¶ 1421.

354. At trial, Amgen only offered a conclusory statement by its expert, Dr. Myerson, that "the inventors were in possession of a crystalline form of apremilast that they could then

identify via XRPD." DFF ¶ 1429. Dr. Myerson did not cite any disclosure in Example 2, in the '515 application, or even outside the four corners of the '515 application to support this assertion. *Id.* As Dr. Myerson admitted, there is none. *Id.* Further, the Federal Circuit has "repeatedly stated that actual possession or reduction to practice outside of the specification is not enough. Rather, [] it is the specification itself that must demonstrate possession." *Ariad*, 598 F.3d at 1352; *see also Allergan*, 796 F.3d at 1309 (finding the district court erred by relaying on "the undisclosed clinical protocol to support its written description determination," and explaining that "[i]t is the disclosures of the applications that count."). Therefore, the Court concludes that Amgen did not show the specification of the '515 application satisfies the written description requirement even assuming for the sake of the argument that, as of March 20, 2002, the named inventors of the '515 application might have been in possession of an apremilast crystalline form, which might have been Form B.

ii. Even If Example 2 Disclosed An Apremilast Crystalline Form, Amgen Has Failed To Show It Would Inherently be Crystalline Form B.

355. The Court finds that the '515 application does not inherently disclose an apremilast *crystalline Form B*. After assuming without support that Example 2 of the '515 application describes a *crystalline* apremilast solid, as opposed to an amorphous form or a mixture, Amgen focuses on arguing that the alleged crystalline solid obtained in Example 2 is inherently Form B. DFF ¶ 1431. The court finds Amgen's arguments unpersuasive.

356. This case does not fall within the "the rare exceptions to the rule that a party must show possession of every feature recited in the [claim] and that every limitation of the claim must have been known to the inventor at the time of the alleged conception." *Hitzeman*, 243 F.3d at 1354–55. For example, "[i]n the context of priority determinations, the allegedly inherent limitation cannot be material to the patentability of the invention." *Id.* at 1355. In

Hitzeman, the Federal Circuit rejected the argument that "particle size and sedimentation rate limitations" were inherent, even though the Federal Circuit agreed that in a scientific sense, once the yeast was transformed by the claimed vector, it would necessarily produce particles having the claimed size and sedimentation rate. *Id.* The Federal Circuit explained this scientific principle "does not mean that the particle size and sedimentation rate limitations are 'inherent' in a legal sense, such that the inventors need not establish specific conception of these features," because these limitations were not redundant of the other limitations and were "central to the patentability and utility of the claimed invention, and it provided the basis for Hitzeman to distinguish his claims from the prior art." *Id.*

357. Here too, like *Hitzeman,* the apremilast crystalline Form B and the XRPD peaks recited in claims 1 and 15 of the '101 patent are not redundant of the enantiomerically pure apremilast limitation and were central to the patentability and utility of the alleged invention claimed in the '101 patent. *See* DFF ¶ 1408. Thus, like *Hitzeman*, the apremilast crystalline Form B and the XRPD peaks recited in claims 1 and 15 are not "inherent in a legal sense" in Example 2 of the '515 application, even if in a scientific sense, following Example 2 would lead to an apremilast crystalline form with these recited limitations (which Amgen has not shown).

358. Further, as explained above, neither Example 2 nor any other part of the '515 application explicitly disclose any description, information, or data about the solid form of the "solid" apremilast obtained in Example 2. Therefore, the Court finds this case does not fall within the narrow set of circumstances where written description was met without an explicit disclosure. In its pretrial briefing, Amgen cited two cases to support its inherent disclosure argument. *See* D.I. 399 at 84 (*citing Yeda Research & Dev. Co. v. Abbott GMBH & Co. KG*, 837

F.3d 1341, 1345 (Fed. Cir. 2016) and *Allergan*, 796 F.3d at 1309). *Allergan* and *Yeda* are both inapposite.

359. In *Allergan*, the Federal Circuit held a claim to a pharmaceutical formulation *explicitly disclosed* in a patent disclosure was not invalid for lack of written description when the claim also recited an inherent property of the formulation that was not explicitly described. *Allergan*, 796 F.3d at 1308–1309. More specifically, the Federal Circuit explained that the patents at issue "describe a formulation comprising 0.01% bimatoprost and 200 ppm BAK as one of the best modes of the invention," and that the claims-at-issue "all require the same amounts of bimatoprost and BAK." Thus "the skilled artisan would immediately discern the claimed formulation in that disclosure." *Id.* The claims-at-issue in *Allergan* also included limitations directed to "the clinical efficacy and hyperemia profile of the claimed formulation," which were not explicitly disclosed. *Id.* at 1309. The Federal Circuit held, "on this particular record," "a claim that recites a property that is necessarily inherent in a formulation *that is adequately described* is not invalid as lacking written description merely because the property itself is not explicitly described." *Id.* (emphasis added).

360. Amgen's reliance on *Allergan* is misplaced. Here, the asserted claims of the '101 patent are directed to crystalline apremilast Form B, having four specific XRPD peaks. DFF ¶¶ 71-73. The '515 application, however, does not explicitly disclose an apremilast *crystalline* form, let alone *Form B*, nor does it explicitly disclose any words, figures, formulas, diagrams, or any other descriptive or analytical information from which a POSA could conclude the named inventors of the '515 application were in possession of an apremilast *crystalline* form, or *Form B*. *Id.* ¶¶ 1411, 1418-1426. As the Federal Circuit has explained, "the hallmark of written description is disclosure." *Ariad*, 598 F.3d at 1351. That the undisclosed apremilast crystalline

Form B inherently has the four XRPD peaks recited in claim 1 does not satisfy the written description requirement in the absence of any explicit disclosure of the claimed apremilast crystalline Form B.

361. *Yeda* is similarly inapposite. In *Yeda*, the Federal Circuit held that a claimed protein was adequately described when the specification *explicitly* disclosed a partial N-terminus sequence along with additional biological characteristics and traits, *and* it was undisputed that the claimed protein was "the only protein with the same partial N-terminus sequence and additional traits disclosed." *Yeda*, 837 F.3d at 1345. Thus, the Federal Circuit explained that the application at issue inherently disclosed the remaining amino acids in the N-terminus sequence of the claimed protein. *Id.* In contrast, here, the '515 application does not explicitly disclose an apremilast *crystalline* form, let alone *Form B*, nor does it explicitly disclose any words, figures, formulas, diagrams, or any other descriptive or analytical information from which a POSA could conclude the named inventors of the '515 application were in possession of an apremilast *crystalline* form, or *Form B*. DFF ¶¶ 1411, 1418-1426. Further, here, it is disputed whether the claimed crystalline Form B is "the only" apremilast solid that could be prepared following the disclosure in Example 2 of the '515 patent. *Id.* ¶¶ 1419, 1427-28, 1433-38, 1441. That the undisclosed apremilast crystalline Form B inherently has the four XRPD peaks recited in claim 1 does not satisfy the written description requirement in the absence of any explicit disclosure of the claimed apremilast crystalline Form B.

362. The Federal Circuit has previously rejected inherency arguments when the explicit disclosure in the specification at issue did not reach the level shown in *Yeda* or *Allergan*. *See, e.g., In re Wallach*, 378 F.3d 1330, 1334–35 (Fed. Cir. 2004) (holding that possession of a DNA molecule did not mean that the applicant possessed the specific amino acid sequence

encoded by that molecule even though the sequence was an inherent property of the DNA molecule). The appellants in *Wallach* "claimed the nucleic acids encoding a protein for which they provided only a partial sequence." *Id.* at 1334. Citing the Patent Office's Manual of Patent Examining Procedure, the Federal Circuit explained "disclosure of a partial structure without additional characterization of the product may not be sufficient to evidence possession of the claimed invention." *Id.* The Federal Circuit then rejected appellants' argument that because they showed they were in possession of the protein at issue, they "were also necessarily in possession of its amino acid sequence," and explained:

> Whether Appellants were in possession of the protein says nothing about whether they were in possession of the protein's amino acid sequence. Although Appellants correctly point out that a protein's amino acid sequence is an inherent property of the protein, the fact that Appellants may have isolated and thus physically possessed [the protein at issue] does not amount to knowledge of that protein's sequence or possession of any of its other descriptive properties.

Id. at 1334–35. Similarly, here, that the named inventors of the '515 application had prepared an apremilast "solid" by purifying an apremilast "residue" via the general purification procedure disclosed in Example 2 (DFF ¶¶ 1418-1420) does not amount to their knowledge of that "solid" form's XRPD pattern, let alone the specific crystalline Form B XRPD peaks recited in claim 1 of the '101 patent. To the contrary, the disclosed information in Example 2 shows that the named inventors of the '515 application were not interested in describing or characterizing the "solid" obtained at the end of Example 2. *Id.* ¶¶ 1421-26. Thus, Amgen did not show that the '515 application inherently disclosed the claimed apremilast crystalline Form B.

363. As explained below, the evidence Amgen presented at trial fell short of the high bar set by the Federal Circuit for showing that the '515 application inherently discloses the claimed apremilast crystalline Form B. It is long established that the alleged inherent aspect

must necessarily occur, that is, a showing that the alleged inherent function, characteristic, or property might occur is insufficient. *See, e.g., Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998) ("In order for a disclosure to be inherent, . . . the missing descriptive matter must necessarily be present in the . . . specification such that one skilled in the art would recognize such a disclosure."); *Agilent Techs., Inc. v. Affymetrix, Inc*., 567 F.3d 1366, 1382–83 (Fed. Cir. 2009) ("The very essence of inherency is that one of ordinary skill in the art would recognize that a reference unavoidably teaches the property in question.").

364. As explained above, Amgen's entire argument for disclosure rests on a partial sentence in Example 2 of the '515 application that states simply that an apremilast "residue [was] recrystallized from a binary solvent containing ethanol (150 mL) and acetone (75 mL)." DFF ¶ 1417. First, the Court finds that a POSA would understand the term "recrystallized" here to describe a process for purifying apremilast prepared by chemical synthesis by precipitating it from the solution, which does not necessarily lead to production of a crystalline solid. *Id.* ¶¶ 1418-20. Further, the partial sentence Amgen relies on leaves out many details about how the named inventors of the '515 application performed the recrystallization step. *Id.* ¶ 1427. The parties agreed that the particular solid form of the "solid" obtained at the end of this recrystallization step depends on the undisclosed details of the recrystallization step. *Id.* ¶¶ 1428, 1433-35. In particular, Amgen's expert, Dr. Myerson, admitted that "the specific crystalline form that is produced using a combination of ethanol and acetone" "can be influenced by the cooling rate." *Id.* ¶ 1435. Instead, the evidence presented at trial showed that following Example 2 does not always lead to the claimed apremilast crystalline Form B—rather it could lead to other crystalline forms, such as Form A or Form C. *Id.* ¶¶ 1433-38, 1441. Thus, the partial sentence Amgen relies on does not inherently disclose the claimed apremilast crystalline

Form B. *See, e.g., Rexnord Industries, LLC v. Kappos*, 705 F.3d 1347, 1354–55 (Fed. Cir. 2013) (inherency was not found due to lack of precision and specificity in the disclosure); *Endo Pharms. Solutions Inc. v. Custopharm, Inc*., 234 F.Supp.3d 587, 600 (D. Del. 2017), aff'd, 894 F.3d 1374, 1381-83 (Fed. Cir. 2018) (finding the presence of benzyl benzoate or its ratio with castor oil was not inherent in the prior art disclosure because of failure to establish that the disclosure barred the possibility of an alternative vehicle being used); *In re Armodafinil Patent Litigation*, 939 F. Supp. 2d at 470 (finding the disclosure at issue was not shown to "necessarily and inevitably result[] in [crystalline] Form I armodafinil," because the evidence presented at trial showed that the disclosure at issue could yield different forms, mixtures of forms, and unknown impurities, depending on the variables selected in conducting the disclosed procedure).

365. The evidence Amgen presented at trial to support its inherent disclosure argument is data from 13 experiments submitted by three generic companies several years after the alleged priority date to the European Patent Office ("EPO") as part of an opposition proceedings. DFF ¶ 1431. There is, however, a dispute between the polymorph experts whether these 13 experiments submitted by the three generic companies were proper replications of Example 2. *Id.*

366. Even if following Example 2 under certain circumstances using undisclosed parameters may lead to apremilast crystalline Form B, that does not show following Example 2 would ***always*** lead to apremilast crystalline Form B. Amgen's expert, Dr. Myerson, admitted that to demonstrate that a disclosure inherently results in an intended outcome, "an example has to always produce the patented, in this case the patented crystal form, every time without exception." DFF ¶ 1432. Amgen, however, did not offer any expert testimony or evidence that the experiments submitted by the three generic companies to the EPO cover ***every*** possible

variation of the recrystallization step generally described in Example 2. *See, e.g., Hansgirg*, 102 F.2d at 212; *Agilent Techs.*, 567 F.3d at 1382–83 ("The very essence of inherency is that one of ordinary skill in the art would recognize that a reference unavoidably teaches the property in question.").

367. Instead, the evidence presented at trial showed that following Example 2 does not always lead to the claimed apremilast crystalline Form B. DFF ¶¶ 1433-37. For example, Celgene and the inventors themselves stated in their '101 patent disclosure that apremilast *Form A* can be obtained from "solvent systems comprising acetone, ethanol, and mixtures thereof," "using a fast cooling crystallization process." *Id.* ¶ 1433. This method provided in the '101 patent falls within the general procedure described in Example 2 of the '515 patent. *Id.* Similarly, Ms. Xu's apremilast polymorph screening report states that Form A "was recrystallized from acetone/ethanol after rapid cooling to 15°C for 105 min," which again uses the same binary solvent system described in Example 2 of the '515 application. *Id.* ¶ 1434. The Court also finds that the testimony of the other polymorph expert in this case, Dr. Sachetti, undermines Amgen's assertion that following Example 2 of the '515 application would inevitably and necessarily lead to apremilast crystalline Form B. In particular, Dr. Sacchetti testified that a POSA following Example 2 would obtain apremilast crystalline Form A. *Id.* ¶ 1441. For this reason alone, the Court concludes that the general procedure described in Example 2 of the '515 application does not inherently disclose the claimed apremilast crystalline Form B. *See, e.g., Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995) (no inherent disclosure where it was shown that the allegedly inherent crystalline form was not produced every time when following the teachings of the reference); *In re Armodafinil Patent Litigation*, 939 F. Supp. 2d at 470 (finding the disclosure at issue was not shown to "necessarily

and inevitably result[] in [crystalline] Form I armodafinil," because the evidence presented at trial showed that the disclosure at issue could yield different forms, mixtures of forms, and unknown impurities, depending on the variables selected in conducting the disclosed procedure).

368. As further evidence, Celgene itself previously represented to the European Patent Office that following Example 2 would lead to apremilast crystalline Form C, not Form B. DFF ¶ 1436. Celgene made these representations on June 23, 2017, before filing the instant suit against the Defendants. *Id.* ¶ 1437. Amgen's expert, Dr. Myerson, attempted to dismiss these representations as "Celgene just made a mistake." *Id.* ¶ 1438. This *post hoc* characterization is, however, contrary to what Celgene represented at the EPO. *Id.* Further, as the patentee, Celgene presumably knew how to perform their own Example 2 procedure. *Id.* ¶ 1436. The Court finds it unreasonable and not credible to argue otherwise.

369. Further, Celgene's representations are imputed and attributable to Amgen. *Eastman Kodak Co. v. Goodyear Tire, & Rubber Co.*, 114 F.3d 1547, 1559 (Fed. Cir. 1997) ("Zimmer's actions prior to the assignment of the patent rights are imputed to Eastman. A patentee cannot avoid the consequences of his laches by transferring the patent."); *ISCO Int'l., Inc. v. Conductus, Inc*., 279 F. Supp. 2d 489, 502-04 (D. Del. 2003) (adopting jury's findings that a patent was unenforceable due to inequitable conduct based on actions of a previous assignee of the patent); *Teradyne, Inc. v. Hewlett-Packard Co*., No. 91-0344, 1994 WL 327213, at *7 n.8 (N.D. Cal. 1994) (finding that the predecessor-in-interest's "conduct and knowledge must as a matter of law be attributed to . . . its successor in interest").

370. The Court finds that the fact that the EPO sided with the generic companies and invalidated the European patent they challenged is not relevant at least because the EPO decision was based on a different legal standard regarding a different legal question—invalidity of the

challenged European patent. DFF ¶ 1439. For this additional reason, the Court concludes that the general procedure described in Example 2 of the '515 application does not inherently disclose the claimed apremilast crystalline Form B. *See, e.g., Glaxo*, 52 F.3d at 1047; *In re Armodafinil Patent Litigation*, 939 F. Supp. 2d at 470.

371. For all the forgoing reasons, the Court concludes that Amgen did not meet its burden of demonstrating that the asserted claims of the '101 patent are entitled to the March 20, 2002, priority date.

B. The Asserted Claims Of The '101 Patent Are Obvious As Of March 27, 2008.

372. The Court find that the asserted claims of the '101 patent are invalid for obviousness as of March 27, 2008. A patent is invalid for obviousness, even "though the invention is not identically disclosed or described" in the art if the differences between the asserted claims and the prior art are "such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a); *see also KSR*, 550 U.S. at 406. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416.

373. An obviousness inquiry requires analysis of the scope and content of the prior art, the level of ordinary skill in the art, the differences between the claimed invention and the prior art, and any relevant objective indicia of obviousness or non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). The Supreme Court requires an "expansive and flexible approach" to the question of obviousness. *KSR*, 550 U.S. at 415.

374. At trial, Defendants' expert, Prof. Steed, testified about applying the *KSR* framework concluding that claims 1 and 15 of the '101 patent would have been obvious in view of the '052 publication and the knowledge of a POSA, or alternatively, in view of the '052

publication, Brittain 1997, the ICH Guidelines, Guillory, Brittain 1999, and the knowledge of a POSA. DFF ¶¶ 1463 (the obviousness legal standard applied); 1400-02 (definition of POSA), 1444-61 (determining the scope and content of the prior art), 1467-90 (finding the prior art motivated a POSA with a reasonable expectation of success to prepare the claimed apremilast crystalline Form B), 1491-93 (finding additional limitations of the asserted claims were obvious or known).

375. The Federal Circuit has held that "the presumption of validity does not relieve the patentee of any responsibility to set forth evidence in opposition to a challenger's *prima facie* case which, if left unrebutted, would be sufficient to establish obviousness." *Novo Nordisk A/S v. Caraco Pharm. Labs, Ltd.*, 719 F.3d 1346, 1353, 1356 (Fed. Cir. 2013) (declining to reverse the district court's obviousness determination).

376. At trial, Amgen did not present any evidence or expert testimony to rebut Defendants' evidence that claims 1 and 15 of the '101 patent are obvious in view of the prior art as of March 27, 2008, nor did Amgen cross examine Prof. Steed on his opinions regarding the state of the art pertinent to the '101 patent as of March 27, 2008, including the teachings of the '052 publication (which published in 2003, before the March 27, 2008 priority date). DFF ¶ 1464; *see the Monolithic Power Sys., Inc. v. O2 Micro Int'l Ltd.*, 558 F.3d 1341, 1350 (Fed. Cir. 2009) (affirming factfinder's finding regarding the prior art teaching a claim limitation that stood "unrebutted"). Thus, the Court finds Defendants' unrebutted *prima facie* case is sufficient to establish obviousness. *Novo Nordisk*, 719 F.3d at 1353, 1356.

377. Amgen also did not present any evidence regarding any objective indicia of nonobviousness (e.g., unexpected results) with respect to the asserted claims of the '101 patent. DFF ¶ 1494. Thus, objective indicia of nonobviousness have no effect on the obviousness of the

claimed crystalline apremilast Form B. *See Horizon Medicines LLC v. Alkem Labs Ltd*., No. CV 18-1014-RGA, 2020 WL 7022591, at *3 (D. Del. Nov. 30, 2020).

1. The Prior Art Motivated A POSA To Perform A Routine Polymorph Screen on The Known Enantiomerically Pure Apremilast Using Known Solvents Ethanol and Acetone.

378. The motivation to combine "need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006).

379. Claim 1 of the '101 patent is directed to the crystalline Form B of enantiomerically pure apremilast, comprising four XRPD peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ. DFF ¶¶ 72, 1462. Claim 15 is directed to a solid pharmaceutical composition comprising the crystalline Form B of enantiomerically pure apremilast recited in claim 1. *Id.* ¶¶ 73, 1462.

380. The Court finds that the '052 publication teaches a POSA to prepare an oral pharmaceutical composition comprising enantiomerically pure apremilast for administration to a patient, including sterile solids (crystalline or amorphous). DFF ¶¶ 1456-1461, 1467. These teachings would have motivated a POSA the "routine task of pharmaceutical pre-formulation" on apremilast to "see what crystalline or amorphous solids it actually forms. So, they could then select amongst them which would be the most appropriate to formulate into a" pharmaceutical formulation. *Id.* ¶ 1468, *see also id.* ¶¶ 1444-1451. Amgen's expert, Dr. Myerson, agrees that based on the teachings of the '052 publication, a POSA would have been "interested in finding a crystalline solid form that met a series of properties, one of which would be polymorphic stability," and to do so, a POSA would have undertaken a polymorph screen. *Id.* ¶ 1468.

381. The Court finds the '052 publication discloses a specific solvent system used in the last step for preparing enantiomerically pure apremilast: a 2:1 mixture of ethanol to acetone used for purifying the crude apremilast residue via recrystallization. DFF ¶¶ 1458, 1469. A POSA would have understood the teachings of the '052 publication regarding solvents as an important factor in "in determining polymorphic outcome," and thus would have been motivated to include this solvent system in the routine polymorph screen as an obvious first step in the polymorph screen because the POSA would have understood. *Id.* ¶¶ 1470-71, *see also id.* 1452. Ms. Xu, a named inventor on the '101 patent, agrees. *Id.* ¶ 1470.

382. Other prior art references, such as Brittain 1997 and the ICH Guidelines, would have motivated a POSA to perform a polymorph screen on the known enantiomerically pure apremilast. DFF ¶¶ 1472-77. A POSA motivated to prepare a solid pharmaceutical composition of apremilast based on the teachings of the '052 publication would have combined the teachings of the '052 publication with Brittain 1997 the ICH Guidelines. *Id.* ¶¶ 1474, 1476.

383. The prior art also taught a POSA how to conduct a polymorph screen. For example, Guillory taught various methods to perform a polymorph screen to prepare pharmaceutically relevant solid forms of a pharmaceutical compound, including what solvents to use—solvents "likely to be encountered during formulation and processing," e.g., solvents used for purification of the pharmaceutical compound. DFF ¶¶ 1478-79, 1488. Dr. Myerson agrees. *Id.* ¶ 1479. In view of the '052 publication and Guillory's teaching, a POSA would have been motivated to perform a polymorph screen using the solvent system disclosed in the '052 publication for purification of enantiomerically pure apremilast (ethanol and acetone). *Id.* ¶¶ 1480-82.

384. The prior art, including Brittain 1999, also taught how to characterize various forms obtained from a polymorph screen of apremilast. DFF ¶¶ 1453-55, 1483-85.

385. Therefore, the Court finds a POSA would have been motivated to perform a routine polymorph screen on the known enantiomerically pure apremilast using known solvents ethanol and acetone, and identify and characterize the pharmaceutically relevant solid forms obtained in view of the '052 publication and the knowledge of a POSA, or alternatively in view of the '052 publication, Brittain 1997, the ICH Guidelines, Guillory, Brittain 1999, and the knowledge of a POSA. DFF ¶ 1486.

386. As explained above, at trial, Amgen did not present any evidence or expert testimony to rebut this conclusion.

2. A POSA Would Have Reasonably Expected To Successfully Prepare Pharmaceutically Relevant Solid Forms Of Apremilast, Including Form B, In A Polymorph Screen Using Known Solvents Ethanol And Aceton.

387. A POSA would have understood the solvent system taught in the '052 publication is an important factor in determining polymorphic outcome and would have reasonably expected to succeed in carrying out a crystallization experiment using the solvent system described in Example 2 of the '052 publication. DFF ¶¶ 1487-88. Indeed, Amgen's expert, Dr. Myerson agrees that a POSA would have reasonably expected to succeed in carrying out a crystallization experiment using the solvent system described in Example 2 of the '052 publication. *Id.* ¶ 1488. Thus, the Court finds a POSA in view of the '052 publication would have reasonably expected to prepare solid forms of apremilast, including apremilast crystalline Form B claimed in claims 1 and 15 of the '101 patent. *Id.* ¶¶ 1487-88.

388. In addition to the '052 publication, the Court finds Guillory's teachings support a POSA's reasonable expectation of success in "isolate[ing] and identify[ing] crystalline forms [of

apremilast] that are likely to arise during the normal course of drug development and storage," including Form B that was reported to be the "most thermodynamically stable anhydrous polymorph." DFF ¶¶ 1489-90.

389. To be sure, a POSA would not have been able to know in advance that Form B would be obtained in a polymorph screen with absolute certainty. But, to show obviousness, "only a reasonable expectation of success, not a guarantee, is needed." *Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1364 (Fed. Cir. 2007). The Court concludes that Defendants have clearly and convincingly shown a reasonable expectation of success.

390. As stated above, at trial, Amgen did not present any evidence or expert testimony to rebut a POSA's reasonable expectation of success.

3. The Remaining Elements of Claims 1 and 15 of The '101 Patent Would Have Been Obvious.

391. The Court finds the remaining element of claim 1 of the '101 patent that recites "an X-ray powder diffraction pattern comprising peaks at about 10.1, 13.5, 20.7, and 26.9 degrees 2θ," is obvious to a POSA in view of the prior art. "[I]nherency may supply a missing claim limitation in an obviousness analysis." *Santarus Inc. v. Par Pharmaceutical Cos. Inc*., 945 F.3d 1184, 1191 (Fed. Cir. 2019); *see also In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (holding that even though the claimed controlled-release formulation and its associated food effect were not disclosed the in prior art, the formulation would have been obvious and the claimed food effect was an inherent property of the obvious formulation). It is undisputed that the XRPD peaks recited above are inherent characteristics of the pure apremilast crystalline Form B. DFF ¶ 1491.

392. Further, in view of the prior art, such as Brittain 1999, a POSA would have routinely performed the XRPD experimentation and observed the recited peaks following the

preparation of Form B crystal form of enantiomerically pure apremilast in a routine polymorph screen. DFF ¶ 1491.

393. The additional limitation of claim 15 that recites "a solid pharmaceutical composition" is explicitly disclosed in the '052 publication. DFF ¶ 1492.

394. As explained above, Amgen did not present any evidence or expert testimony to rebut the obviousness of the additional limitations of claims 1 and 15.

395. Therefore, the Court concludes claims 1 and 15 of the '101 patent would have been obvious as of March 27, 2008, in view of the '052 publication and the knowledge of a POSA, as well as in view of the '052 publication, Brittain 1997, the ICH Guidelines, Guillory, Brittain 1999, and the knowledge of a POSA. DFF ¶ 1493.

V. Zydus's ANDA Product Does Not Infringe the Asserted Claims of the '101 Patent.

396. Plaintiffs bear the burden of proving infringement by a preponderance of the evidence. *See Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1336 (Fed. Cir. 2015) (internal citation omitted).

397. A patent infringement analysis involves two steps: (1) construing the claims; and (2) the application of the construed claim to the accused process or product. *See Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 384 (1996); *Amgen Inc. v. Hoescht Marion Roussel, Inc.*, 314 F.3d 1313, 1324 (Fed. Cir. 2003); *Hospira, Inc. v. Amneal Pharm., LLC*, 285 F. Supp. 3d 776, 784-85 (D. Del. 2018). The second step—application of the construed claims to the accused product—is a question of fact. *See Markman*, 517 U.S. at 384.

398. A dependent claim contains all of the limitations of the claim from which it depends. *See Cognex Corp. v. Int'l Trade Comm'n*, 550 Fed. Appx. 876, 881 (Fed. Cir. 2013); *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (citing *Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1552 n.9 (Fed. Cir. 1989)). Accordingly, if a

product does not infringe an independent claim, the product also does not infringe any dependent claim. *Id.*

399. When generic drug applicants file an Abbreviated New Drug Application ("ANDA") to sell a generic version of a branded drug, the infringement inquiry is "properly grounded in the ANDA application and the extensive materials typically submitted in its support." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1248 (Fed. Cir. 2000) (quoting *Glaxo, Inc. v. Novopharm Ltd.*, 110 F.3d 1562, 1569 (Fed. Cir. 1997) ("*Glaxo I*")); *Ben Venue Labs., Inc. v. Novartis Pharm. Corp.*, 146 F. Supp. 2d 572, 580 (D.N.J. 2001). The inquiry must always focus on the product the ANDA applicant will likely sell if the ANDA application is finally approved by the U.S. Food and Drug Administration ("FDA"). *Ferring B.V. v. Watson Laboratories, Inc.*, 764 F.3d 1401, 1408-1409 (Fed. Cir. 2014). This necessarily elmeans that, because drug manufacturers are bound by strict statutory provisions to sell only those products that comport with an ANDA's description of the drug product to be sold, the actual ANDA specifications normally will directly resolve the infringement question because those specifications define a proposed generic product that the ANDA applicant will sell if the ANDA is approved. *Id.*

A. Direct Infringement.

400. Direct infringement requires that the alleged infringer "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent . . . ." 35 U.S.C. § 271(a).[1]

[1] Title 35 of the U.S. Code was amended by the America Invents Act ("AIA"), Pub. L. No. 112-29. However, because the patents-at-issue have effective filing dates prior to the March 16, 2013 effective date of the AIA, those revisions do not apply and the pre-AIA version of Title 35 applies.

401. To prove literal infringement, the patentee must show that every limitation of the asserted claim is literally met by the accused product. *See, e.g., Bayer AG*, 212 F.3d at 1246. Therefore, if the Court finds that the accused product fails to meet even one claim limitation, there can be no literal infringement. *See, e.g., id.; Spectrum Int'l, Inc. v. Sterilite Corp.*, 164 F.3d 1372, 1381 (Fed. Cir. 1998).

402. A claim to a certain crystal form (or polymorph) of drug compound that recites spectral peaks (e.g. XRPD) in the claim requires proof by a preponderance of evidence that each of those peaks is present in the accused product. *See, e.g., Zenith Labs. Inc, v, Bristol-Myers Squibb Co.*, 19 F.3d 1418, 1424 (Fed. Cir. 1994) (reversing finding of infringement based on finding only 22 of 37 claimed peaks); *Glaxo I* at 1566 (affirming non-infringement holding because patentee only showed that only 1 of 29 claimed peaks was present in accused product and "it is elementary patent law that all limitations are material."); *Glaxo Grp. Ltd. v. TorPharm, Inc.*, 153 F.3d 1366, 1374 (Fed Cir. 1998).

403. The level of proof required to prove infringement of a claim to a polymorphic form is ultimately dependent on the specific patent and claim language. Where a claim includes, either expressly or through construction, reference to data limitations like XRPD peaks, courts have found that defendants do not infringe where there is only minimal and circumstantial evidence of the claimed form, especially when such evidence can be interpreted as having a noninfringing origin. *See, e.g.*, *Roche Palo Alto LLC v. Ranbaxy Labs. Ltd.*, 2009 WL 3261252, *36-37 (D.N.J. Sept. 30, 2009) (holding that patentee failed to prove infringement when its testing showed the accused product only had one of the multiple "defining" XRPD peaks and that peak could be attributable to other ingredients in the accused product), *vac'd after settling on appeal*; *Abbott Labs. v. Sandoz, Inc.*, 486 F. Supp. 2d 767, 770, 773 (N.D. Ill. 2007) (holding a

XRPD "peak" must have an "intensity measurement greater than measurements attributable to noise," which are the signals that "cannot be associated with a scientifically significant quantity of the material" being tested); *Schering Corp. v. Apotex Inc.*, Case No. 09-cv-06373, 2012 WL 2263292 (D.N.J. June 15, 2012) (holding patentee failed to prove infringement because its expert failed to compare at least three unique XRPD peaks), *aff'd per curiam*, 517 Fed. Appx. 939 (Fed. Cir. 2013); *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1346-47 (Fed. Cir. 2005) (finding infringement of a claim to "[c]rystalline paroxetine hydrochloride hemihydrate" where manufacture of the accused infringing product *necessarily* created the patented compound; but affirming claim was invalid for inherent anticipation); *cf. Bristol-Myers Squibb Co. v. Mylan Pharmaceuticals Inc.*, Case No. 09-cv-651-LPS, 2013 WL 12322088, *11-12 (D. Del. Oct. 17, 2013) (finding prior art crystal form showing only 4 peaks did not meet claim limitation requiring 6 or more XRPD peaks).

404. Expired samples are not representative of the ANDA product and therefore not relevant to the infringement inquiry. "[I]nfringement under 35 U.S.C. § 271(e)(2) 'must focus on what the ANDA applicant will likely market if its application is approved.'" *Merck Sharp & Dohme Corp. v. Amneal Pharm. LLC,* 881 F.3d 1376, 1385 (Fed. Cir. 2018) (quoting *Glaxo I*, at 1569). Evidence or allegations of what *could* happen to a product after its sale, or what *could* happen to a product when exposed to conditions outside the specified packaging and storage conditions, is not representative of the ANDA product itself, and therefore not relevant to the infringement inquiry. An accused product does not infringe if it does not infringe in its normal state, even if it may be altered into an infringing state under unusual circumstances. *High Tech Medical Instrumentation, Inc. v. New Image Industries, Inc.,* 49 F.3d 1551, 1556 (Fed. Cir. 1995), *citing with approval, Doorking, Inc. v. Sentex Sys.,*

Inc., 19 Fed. Appx. 872, 878 (Fed. Cir. 2001). Thus, in evaluating the relevance of a sample, "the critical inquiry is whether it is representative of what is likely to be approved and marketed." *Id.* By definition, expired samples do not meet the ANDA specification and, therefore, are not representative of the ANDA product that an ANDA applicant will market if its application is approved. *See id.* (looking to the ANDA specification to evaluate whether samples are representative of the ANDA product). For that reason, "evidence derived from expired tablets is not relevant to the question of what will be sold." *SmithKline Beecham Corp. v. Apotex Corp.,* 98 C 3852, 2002 WL 1613724, at *2 (N.D. Ill. July 17, 2002).

405. Zydus's internal testing, as contained in its ANDA, shows that neither Zydus's proposed ANDA products, nor the API contained therein, as they will be sold in the United States, contain crystalline apremilast Form B. *See id*; DFF ¶ 1631.

406. Plaintiff's experts have failed to show that the apremilast in Zydus's proposed ANDA product, as it will be offered for sale, sold, used, and distributed, more likely than not contains crystalline apremilast Form B as claimed and described in the '101 patent. *See Ferring*, 764 F.3d at 1408; *see also Spectrum Pharm*, 802 F.3d at 1336; *Glaxo I* at 1566; DFF ¶¶ 1606-29. Dr. Gozzo's testing presents no evidence that apremilast Form B is present in representative samples of Zydus's proposed ANDA product. *See Merck Sharp & Dohme Corp.*, 881 F.3d at 1385; *SmithKline Beecham*, 98 C 3852, 2002 WL 1613724, at *2; DFF ¶¶ 1614-29. Dr. Myerson has identified no Zydus internal document contradicting the conclusion that the apremilast in Zydus's proposed ANDA product is solely Form A. DFF ¶ 1631. The only evidence of what crystalline form of apremilast is present in what Zydus would actually make and sell is Zydus's internal testing. *Id.* This testing shows that what Zydus would make and sell contains Form A and shows no evidence of Form B. *Id.*

407. Dr. Myerson and Dr. Gozzo have failed to present evidence that Zydus's proposed ANDA product more likely than not contains apremilast Form B. DFF ¶¶ 1606-29. Dr. Myerson bases his infringement opinions on Dr. Gozzo's test results for expired samples that were not shown to be representative of what Zydus would sell. *See Merck Sharp & Dohme Corp.*, 881 F.3d at 1385; *Ferring*, 764 F.3d at 1408; *see also Guidance for Industry: Development of Abbreviated New Drug Applications During the COVID-19 Pandemic – Questions and Answers* (Apr. 5, 2021) available at: https://www.fda.gov/media/147355/download at 4; DFF ¶¶ 1609-13.

408. As the asserted claims of the '101 patent require crystalline apremilast Form B having four XRPD peaks, Amgen must point to all four peaks in a diffractogram of a representative sample of Zydus's proposed ANDA products, and all four of the peaks must be attributable to Form B. *See Zenith Labs.*, 19 F.3d at 1423-24; *Glaxo I* at 1566; DFF ¶ 1607. Dr. Myerson, however, can point to no peaks in Dr. Gozzo's tests or Zydus's internal tests, that can be attributed to Form B and not Form A and/or Form F. *See Roche Palo Alto*, 2009 WL 3261252, *36-37; DFF ¶¶ 1607, 1614-29. As Dr. Miller explained, Amgen has not accounted for the possible presence of Form F or any other form of apremilast that may have peaks coincident with those of Form B in the samples tested by Dr. Gozzo. DFF ¶¶ 1620-28. It is legally inaccurate to attribute peaks to one form of apremilast that are coincident with other forms of apremilast unless one form is known with certainty to be present, then the peaks should be attributed to the form known to be present. *Id.*; DFF ¶ 1626. As Dr. Miller explained, Dr. Myerson's assertion that peaks, allegedly attributable to Form B, can be "hidden" below the limit of detection is based on incorrect science and does not meet the standard for infringement set out

in *Zenith* that all claim limitations must be present. *See Zenith Labs.*, 19 F.3d at 1423-24; DFF ¶ 1618.

409. The significant overlap between the diffractograms and peak lists of Forms A, B, and F renders it impossible to conclude that Form B is present in the samples tested by Dr. Gozzo. *Id.*; DFF ¶¶ 1614-29.

410. Amgen's experts failed to identify all four required XRPD peaks in any diffractogram. DFF ¶¶ 1607, 1614-29. Dr. Gozzo did not test, nor even had access to, representative samples of Zydus's proposed ANDA product or API. *See Merck Sharp & Dohme Corp.,* 881 F.3d at 1385; DFF ¶¶ 1606, 1609. It is legally insufficient to identify a polymorph based on a single peak (or even two peaks) in a diffractogram. *Id.*; DFF ¶ 1623. Dr. Myerson pointed to no peak in Zydus's internal testing data purportedly corresponding to Form B. DFF ¶ 1631.

411. The samples that Dr. Gozzo tested were expired. DFF ¶¶ 1609-10. It is undisputed that there was a large temporal gap between the date on which Plaintiffs received samples of Zydus's proposed ANDA product and API and the dates of Dr. Gozzo's testing. *Id.* Amgen waited more than ten months after the tablets expired before they arranged to ship the tablets to Dr. Gozzo, who tested the tablets about a month later. *Id.* Therefore, Zydus's proposed ANDA product and API samples were tested at least two and a half years and more than ten months past their retest/expiration dates, respectively. *Id.* There is no evidence in the record that the Zydus samples that were held by Covington for a year and a half were representative of what Zydus would make or sell. *See Merck Sharp & Dohme Corp.*, 881 F.3d at 1385; *Ferring*, 764 F.3d at 1408; DFF ¶¶ 1611-13. No legal or scientific conclusion can be

drawn from this testing of unrepresentative samples. *See SmithKline Beecham,* 98 C 3852, 2002 WL 1613724, at *2; DFF ¶ 1613.

412. Based on this decision to test samples never proven to meet the Federal Circuit's standard for ensuring relevance to the dispositive issue of infringement, the Court should give no weight to Dr. Gozzo's XRPD testing or any of Dr. Myerson's testimony regarding its results. DFF ¶¶ 1606-29.

413. Peaks cannot be "hidden" within a diffractogram—they are either present or not present. *See Abbott Labs*, 486 F. Supp. 2d at 770, 773; DFF ¶ 1618.

414. The Court finds Amgen did not meet its burden of proving that Zydus's proposed ANDA product, as it will be sold, would infringe claims 1 and 15 of the '101 patent by a preponderance of the evidence. DFF ¶¶ 1606-31.

VI. The Asserted Claims Of The '283 Patent Are Invalid.

415. A patent is presumed valid and invalidity must be proven by clear and convincing evidence. *See* 35 U.S.C. § 282; *see also Microsoft Corp. v. i4i Partnership*, 564 U.S. 91, 95 (2011).

416. Clear and convincing evidence "place[ ] in the fact finder 'an abiding conviction that the truth of [the] factual contentions are highly probable.'" *Impax Laboratories v. Lannette Holdings Inc.*, 893 F.3d 1372, 1378 (Fed. Cir. 2018); *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S.Ct. 2433 (1984)) (second alteration in original).

A. Person Of Ordinary Skill In The Art.

417. A patent and its prior art are viewed through the eyes of a person of ordinary skill in the art ("POSA") at the time the invention was made. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). The person of ordinary skill in the art is a legal construct—a

hypothetical person who is presumed to know all of the relevant prior art. *See In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995); *Union Carbide Corp. v. Am. Can Co.*, 724 F.2d 1567, 1576 (Fed. Cir. 1984) (describing the POSA as "the inventor working in his shop with the prior art references—which he is presumed to know—hanging on the walls around him"). "A person of ordinary skill is also a person of ordinary creativity, not an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007).

418. "Factors that may be considered in determining level of ordinary skill in the art include: (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." *Daiichi Sankyo Co., Ltd. v. Apotex Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007) (internal quotation and citations omitted); *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 666–67 (Fed. Cir. 2000). "Not all such factors may be present in every case, and one or more . . . may predominate." *Envtl. Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 696-97 (Fed. Cir. 1983).

419. Where an issue calls for consideration of evidence from the perspective of one of ordinary skill in the art, a witness may not testify on the issue unless qualified as a technical expert in that art. *See Sundance, Inc. v. DeMonte Fabricating Ltd.*, 550 F.3d 1356, 1363 (Fed. Cir. 2008); *see also generally Sloan Valve Co. v. Zurn Indus., Inc.*, No. 10-cv-00204, 2013 WL 6068790, at *7 (N.D. Ill. Nov. 18, 2013) ("The majority of Dr. Magee's opinions regarding obviousness are based on the perspective of a [POSA]. Because he is not a [POSA], he is not qualified to give these opinions.").

420. A POSA with respect to the claimed subject matter of the '283 patent would include a person who possesses an advanced degree (e.g., Master's degree or Ph.D., or foreign

equivalents of either of the foregoing) in the fields of solid state chemistry or a related discipline, such as physical chemistry or pharmaceutical science, and several years of experience in the pertinent field. A POSA could have a lower level of formal education, such as a Bachelor's degree, if such a person had more years of experience in the field of pharmaceutical science or solid state chemistry. DFF ¶ 1721.

421. A POSA would have worked as part of a team that included one or more other people of ordinary skill in the art with respect to one or more other aspects of the claims of the patents. The other people of ordinary skill in the art would have expertise and knowledge obtained through his or her educational, industrial, or academic experiences, including specialties in medicinal chemistry, organic or synthetic chemistry, pharmaceutical formulation, pharmacology, medicine, and clinical use. DFF ¶ 1722.

422. The '283 is invalid for obviousness whether the Court adopts Dr. Sacchetti's or Dr. Myerson's definition of a POSA. DFF ¶ 1723.

B. Anticipation.

423. A person is not entitled to a patent if "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent," 35 U.S.C. § 102(a), or "the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States," 35 U.S.C. § 102(b).

424. A person is not entitled to a patent if "the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have

the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language." 35 U.S.C. § 102(e).

425. A patent claim is anticipated (*i.e.*, not novel) if comparison of the claim with a prior art reference reveals that every element of the claim is described, either expressly or inherently, in the prior art reference. *Apotex*, 754 F.3d at 958 (citing *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003)); *Union Oil Co. of Cal. v. Atl. Richfield Co.*, 208 F.3d 989, 994-95 (Fed. Cir. 2000); *Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1363 (Fed. Cir. 1998).

426. Either a single element of claimed subject matter or the entire claimed subject matter may be inherently disclosed. *Schering*, 339 F.3d at 1379. Inherency arises when a limitation not expressly found in a prior art reference is necessarily present based on what the prior art reference conveys to those of ordinary skill in the art. *See Baxter*, 471 F.3d at 1368. "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *Mehl/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999); *see also Schering*, 339 F.3d at 1377, 1379.

427. A reference includes an inherent characteristic if that characteristic is the "natural result" flowing from the reference's explicitly recited teachings. *See Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001). Thus, a compound (and therefore its inherent physical properties) may be deemed to have been inherently disclosed by a reference that teaches the manner by which that compound would have been made. *See Schering*, 339 F.3d at 1373, 1380; *see also Smithkline*, 403 F.3d at 1345. Newly discovered results of known processes are inherent and unpatentable. *See Bristol-Meyers Squibb Co.*, 246 F.3d at 1376.

428. "[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference." *Schering*, 339 F.3d at 1377 (citing *Cont'l Can*, 948 F.2d at 1268). "[I]nherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure." *Id*. (citing *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1351 (Fed. Cir. 2002)). This means evidence that was unavailable on the critical date can be used to support a defense of patent invalidity based on inherency. *Schering*, 339 F.3d at 1377. Disclosure of a definite and limited class of compounds is sufficient disclosure for anticipation of each member of the class that a person of ordinary skill in the art would envisage from reading the prior art reference. *In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962).

429. A prior art reference can be enabled for purposes of anticipation even if the disclosed embodiment was not actually made, and even if there is no evidence that the disclosed compound works for its intended purpose. *In re Gleave*, 560 F.3d 1331, 1334-36 (Fed. Cir. 2009) ("A thorough reading of our case law, however, makes clear that a reference need disclose no independent use or utility to anticipate a claim under § 102."); *Schering*, 339 F.3d at 1380; *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985). Indeed, the standard used to determine whether prior art provides an enabling disclosure under 35 U.S.C. § 102 is much less stringent than the test that must be employed with regard to 35 U.S.C. § 112. *See Gleave*, 560 F.3d at 1334-36 (Fed. Cir. 2009) (a prior-art reference may be enabling for the purposes of anticipation even if it would not "otherwise entitle its author to a patent" under the enablement requirement of 35 U.S.C. § 112).

430. Prior art references are presumed to be enabled. *See Proctor & Gamble Co. v. Nabisco Brands, Inc*., 711 F. Supp. 759, 772 (D. Del. 1989) (finding that P&G failed to meet its burden to show that the prior art was not enabling).

431. The Court finds claims 2 and 27 of the '283 patent are proven to be anticipated by the '052 publication by clear and convincing evidence. *See Allergan*, 754 F.3d at 958; DFF ¶¶ 1706-19.

432. Taking Amgen's patent specification at its word (given under oath) as a POSA and this Court must, practicing the single example for making enantiomerically pure apremilast taught in both the '052 publication and the '283 patent would inherently and necessarily result in formation of crystalline apremilast Form A. *See* 35 U.S.C. § 282 (presumption of validity); *see also Hoechst Marion Roussel, Inc.*, 314 F.3d at 1355 (both the claimed and unclaimed disclosures in a patent specification are presumed be enabled); DFF ¶¶ 1707-14.

433. A POSA would have recognized that repeating Example 2 of the '052 publication would recrystallize enantiomerically pure apremilast in a mixture of ethanol and acetone by fast cooling. DFF ¶¶ 1707-14. Amgen's own '283 patent teachings expressly tell a POSA that this very process yields apremilast Form A. DFF ¶¶ 1707-14.

434. The explicit teachings in the '283 patent specification are presumed to be accurate under the patentees' duty of candor to the United States Patent and Trademark Office and the public at large when obtaining their patent monopoly. 37 C.F.R. § 1.56 (Duty to disclose information material to patentability).

435. The Court must also assume the teachings of the patent to be true, unless shown by an opponent to be inaccurate by clear and convincing evidence. 35 U.S.C. § 282(a); *see also*

Microsoft Corp. v. I4I Ltd. P'ship, 564 U.S. 91, 95 (2011). Amgen has not shown the teachings of the '283 patent to be false by clear and convincing evidence. DFF ¶¶ 1715-16.

436. A POSA would have understood that the '052 publication and '283 patent contain the same teachings as to formulating stereomerically or enantiomerically pure apremilast into pharmaceutical compositions. DFF ¶ 1707.

437. Celgene's represented to the Patent Office (under oath) that the process as taught in Example 2 of the '052 publication and the '283 patent would inevitably yield enantiomerically pure apremilast Form A. DFF ¶ 1707. Amgen inherited, and cannot escape, these representations when it was assigned the '283 patent. *Id.*

438. A POSA would have understood that the '052 publication teaches a method of making enantiomerically pure apremilast in Example 2: recrystallization from a solution of 2:1 ethanol/acetone. *See Allergan*, 754 F.3d at 958; DFF ¶¶ 1707-08.

439. A POSA would have understood that the '052 publication provides for recrystallization of enantiomerically pure apremilast from 2:1 mixture of ethanol and acetone. A POSA would understand this process to be a typical recrystallization. DFF ¶ 1708. A POSA would have understood this recrystallization as consistent with "fast cooling." *See Schering*, 339 F.3d at 1377; DFF ¶ 1708.

440. Example 2 in the '052 publication, as practiced by a POSA, would inevitably yield Form A as a result of fast cooling from a mixture of ethanol and acetone. *See Schering*, 339 F.3d at 1377; DFF ¶ 1708.

441. The Court concludes claim 2 of the '283 patent is anticipated because Example 2 of the '052 publication inherently discloses crystalline apremilast Form A, and the XRPD pattern

and 5 peaks listed in claim 2 are inherent properties of Form A. *See Schering*, 339 F.3d at 1377; DFF ¶¶ 1706-12.

442. A POSA would have understood the '052 publication to teach the utility of apremilast for treatment of various diseases including psoriasis. *See Allergan*, 754 F.3d at 958; DFF ¶ 1713.

443. The Court concludes claim 27 of the '283 patent is anticipated because the '052 publication inherently discloses Form A and teaches pharmaceutical compositions of enantiomerically pure apremilast comprising Form A. *See Schering*, 339 F.3d at 1377; DFF ¶ 1714.

C. Obviousness.

444. "A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); *see also KSR*, 550 U.S. at 427 ("the results of ordinary innovation are not the subject of exclusive rights under the patent laws").

445. "Obviousness under 35 U.S.C. § 103(a) is ultimately a legal question, based on underlying factual determinations." *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008). "The factual determinations underpinning the legal conclusion of obviousness include 1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness." *Id.* (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966)).

446. A patent is invalid if it is proven to be obvious by clear and convincing evidence. *See, e.g.*, *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1193 (Fed. Cir. 2014); *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 993–94 (Fed. Cir. 2009).

447. Obviousness is demonstrated when "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Procter & Gamble*, 566 F.3d at 994.

448. The fact that a reference was previously considered by the PTO does not increase the burden of proof or preclude a finding of invalidity but merely speaks to the weight of that reference's evidence. *See Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259-1260 (Fed. Cir. 2012) ("Whether a reference was previously considered by the PTO, the burden of proof is the same: clear and convincing evidence.") (citing *Microsoft Corp. v. i4i Ltd. P'ship*, 131 S. Ct. 2238, 2245-46 (2011)). A finding of invalidity may be appropriate where the reference was considered by the PTO, but the examiner failed to give proper consideration to the teachings of that reference. *See Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1366 (Fed. Cir. 2007).

449. The Court concludes that claims 2 and 27 of the '283 patent are shown to be obvious over the '052 publication in view of Fieser, Guillory, and Byrn 1994 as well as the general knowledge of a POSA by clear and convincing evidence. *See KSR*, 550 U.S. at 427.

1. Scope And Content Of The Prior Art.

450. The scope of the prior art includes art that is "reasonably pertinent to the particular problem with which the inventor was involved." *In re GPAC Inc.*, 57 F.3d 1573, 1577 (Fed. Cir. 1995) (citation omitted). In determining whether the claimed invention falls within the scope of the relevant prior art, a court first examines, "the field of the inventor's endeavor" and

"the particular problem with which the inventor was involved" at the time the invention was made. *Princeton Biochemicals*, 411 F.3d at 1339. "A reference is reasonably pertinent if, even though it may be in a different field of endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *Id.* (citation omitted).

451. In determining obviousness, printed publications, patents, and patent applications all constitute prior art under 35 U.S.C. § 102. Specifically, art is prior art under § 102(a) if it was "patented" or "described in a printed publication . . . before the effective filing date of the claimed invention." 35 U.S.C. § 102(a); *see also Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1576 (Fed. Cir. 1996) ("under section 102(a), a document is prior art only when published before the invention date.").

452. A reference is prior art under § 102(b) if it was "patented or described in a printed publication . . . one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b).

453. A published patent application is prior art under § 102(e) if it was filed by another before the invention by the applicant for the patent. A patent granted on an application for patent by another filed in the United States before the invention by the applicant for the patent is also prior art under § 102(e).

454. Prior art references in an obviousness evaluation must be considered as a whole and are not limited to the particular invention they describe. *See, e.g.*, *Belden Inc. v. Berk-Tek LLC*, 805 F.3d 1064, 1076 (Fed. Cir. 2015) (*citing EWP Corp. v. Reliance Universal, Inc.*, 755 F.2d 898, 907 (Fed. Cir. 1985) ("A reference must be considered for everything it teaches by way of technology and is not limited to the particular invention it is describing and attempting to

protect."). This is true even if a particular embodiment of the invention is not the preferred embodiment. *See, e.g.*, *In re Arora*, 2010 WL 816569, at *2 ("Dr. Arora argues that Andersson should be understood as limited to the narrow teaching that a smaller amount of a drug is needed when delivered via Andersson's inventive dry powder inhaler instead of a metered dose inhaler. It is well-settled, however, that a prior art reference must be considered for all that it teaches to those of ordinary skill in the art, not just the embodiments disclosed therein. Andersson teaches the broad principle that different drugs are equipotent at different dosages, and even provides an example of that principle."); *Purdue Pharma Prods., L.P. v. Par Pharm., Inc.*, Nos. 2009-1553, 2009-1592, 2010 WL 2203101, at *3 (Fed. Cir. 2010) ("[Prior art reference] renders the selection of tramadol obvious regardless of whether or not the patent lists tramadol as a preferred embodiment.").

455. While the cited prior art as a whole must enable a POSA to make and use the apparatus or method, each individual prior art reference is prior art, regardless of whether it alone provides an enabling disclosure. *See ABT Sys.*, 797 F.3d at 1360 n.2 (; *Geo M. Martin, Co. v. Alliance Mach. Sys. Int'l*, *LLC*, 618 F.3d 1294, 1302–03 (Fed. Cir. 2010); *Therasense, Inc. v. Becton, Dickinson and Co.*, 593 F.3d 1289, 1297 (Fed. Cir. 2010) (vacated for en banc rehearing on inequitable conduct).

456. Additionally, prior art references may be combined with the knowledge and/or experience of a POSA to "fill in the gap when limitations of the claimed invention are not specifically found in the prior art." *Belden Techs., Inc. v. Superior Essex Commc'ns LP*, 802 F. Supp. 2d 555, 563 (D. Del. 2011) (*citing Purdue Pharma Prods., L.P. v. Par Pharm., Inc.*, 642 F. Supp. 2d 329, 360 (D. Del. 2009); *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (Fed. Cir. 2013)

("[T]he knowledge of such an artisan is part of the store of public knowledge that must be consulted when considering whether a claimed invention would have been obvious.").

457. "What a reference teaches a [POSA] is not . . . limited to what a reference specifically 'talks about' or what is specifically 'mentioned or 'written' in the reference." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005).

458. Also, a determination that a claimed invention would be obvious, therefore "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418.

a. The '052 Publication.

459. The '052 publication is prior art to the '283 patent. *See In re GPAC*, 57 F.3d at 1577. For a discussion of the relevant disclosures of the '052 publication, *see* ¶¶ 436-443.

b. Fieser.

460. Fieser is prior art to the '283 patent. *See In re GPAC*, 57 F.3d at 1577. A POSA would have understood Fieser to teach common crystallization and recrystallization techniques relevant to organic compound, including pharmaceutical compounds. *See Belden*, 805 F.3d at 1076; DFF ¶¶ 1725-26.

c. Byrn 1994.

461. Byrn 1994 is prior art to the '283 patent. *See In re GPAC*, 57 F.3d at 1577. A POSA would have understood Byrn 1994 to teach a variety of factors that influence polymorphic form obtained during crystallization or recrystallization, including seeding. *See Belden*, 805 F.3d at 1076; DFF ¶ 1727. A POSA would have further understood Byrn 1994 to teach that polymorphs can be uniquely identified by their X-ray powder diffraction pattern. *See Belden*, 805 F.3d at 1076; DFF ¶ 1727.

d. Guillory.

462. Guillory is prior art to the '283 patent. *See In re GPAC*, 57 F.3d at 1577. A POSA would have understood Guillory to teach the necessity of conducting polymorph screens during pharmaceutical development. *See Belden*, 805 F.3d at 1076; DFF ¶ 1728. A POSA would have further understood Guillory to teach a number of screening methods useful in the identification of polymorphs, including the use of fast cooling. *See Belden*, 805 F.3d at 1076; DFF ¶ 1730.

2. Differences Between The Claimed Invention And The Prior Art.

463. In determining the differences between the claimed invention and the prior art, obviousness is judged under "an expansive and flexible approach" driven by "common sense." *KSR*, 550 U.S. at 401, 403; *see also id.* at 421 (finding that the Federal Circuit "drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias," because "[r]igid preventative rules that deny factfinders recourse to common sense . . . are neither necessary under our case law nor consistent with it."); *Senju Pharm. Co. Ltd. v. Apotex Inc.*, 836 F. Supp. 2d 196, 208 (D. Del. 2011) ("The Supreme Court has emphasized the need for courts to value common sense over rigid preventative rules . . . .") (citation omitted).

464. In making this determination, the court must consider both the claimed invention and the prior art as a whole in light of the court's construction of the claims at issue. *See Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1479-80 (Fed. Cir. 1998) ("In determining obviousness, the invention must be considered as a whole and the claims must be considered in their entirety.").

465. "For obviousness, a single reference need not disclose every element of the claimed invention." *See, e.g.*, *Hospira, Inc. v. Amneal Pharm., LLC*, 285 F. Supp. 3d 776, 783 (D. Del. 2018) (citing *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007)).

466. "While it may be easier to prove obviousness if each limitation of the claimed invention is found in the prior art, the level of skill of one of ordinary skill in the art can, at times, fill in the gap when limitations of the claimed invention are not specifically found in the prior art." *Belden Techs.*, 802 F. Supp. 2d at 563.

467. A conclusion of obviousness may be based on a single reference or a combination of prior art references. *See Senju Pharm.*, 836 F. Supp. 2d at 208 ("[A] defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed."); *see also In re Merck & Co., Inc.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("We see no clear error in the Board's determination as to the teachings of the prior art references, in combination.").

468. Where the issue of obviousness is based on a combination of elements, a claim is invalid for obviousness if "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention." *Pfizer*, 480 F.3d at 1361.

469. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416; *see also Q.I. Press Controls, B.V. v. Lee*, 752 F.3d 1371, 1379 (Fed. Cir. 2014) (same). This is because "[g]ranting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility." *KSR*, 550 U.S. at 402; *id.* at 427 ("We build and create by bringing to the tangible and palpable reality around us new works based on instinct, simple logic, ordinary inferences, extraordinary ideas, and sometimes even genius. These advances, once part of our shared knowledge, define a new threshold from which

innovation starts once more. And as progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws.").

470. "Obviousness exists when 'a finite, and in the context of the art, small or easily traversed, number of options . . . would convince an ordinarily skilled artisan of obviousness.'" *Purdue Pharma*, 642 F. Supp. 2d at 368 (*quoting Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008)); *see also C.W. Zumbiel*, 702 F.3d at 1387 (finding obviousness where the invention involved "no more than the exercise of common sense in selecting one out of a finite—indeed very small—number of options"). In such a case, an invention is considered "obvious to try." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1332 (Fed. Cir. 2014) (finding claimed dosage obvious to try). Further, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill." *KSR*, 550 U.S. at 401. "When the prior art provides the means of making the invention and predicts the results, and the patentee merely verifies the expectation through 'routine testing,' the claims are obvious." *Purdue*, 642 F. Supp. 2d at 368 (*citing Pfizer*, 480 F.3d at 1367).

471. "Obviousness does not require absolute predictability of success"; rather, "[a]ll that is required is a reasonable expectation of success" in making the invention via the combination. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation omitted); *see also Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 Fed. Appx. 289, 294 (Fed. Cir. 2011) ("[T]here is no requirement that a teaching in the prior art be scientifically tested or even guarantee success before providing a reason to combine. Rather, it is sufficient that one of

ordinary skill in the art would perceive from the prior art a reasonable likelihood of success.") (citations omitted).

472. The Federal Circuit "has long rejected a requirement of '[c]onclusive proof of efficacy' for obviousness." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018) (and cases cited therein).

473. Requiring testing for every possible configuration or combination in the prior art "improperly equates a reasonable expectation of success with absolute certainty." *See, e.g.*, *Hospira*, 285 F. Supp. 3d at 794 (citation omitted).

474. Prior to *KSR*, the Federal Circuit imposed a rigid "teaching-suggestion-motivation" test for obviousness. Under this test, the patent challenger was required to prove that "some motivation or suggestion to combine the prior art teachings" could be found "in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art." *KSR*, 550 U.S. at 407. The Supreme Court in *KSR* rejected the Federal Circuit's test in favor of a more flexible obviousness standard, stating that "the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *Id.* at 418.

475. This more flexible standard expands the obviousness analysis beyond just "published articles and the explicit content of issued patents." *Id.* at 419. In broad terms, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420; *see also Perfect Web Tech., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1329 (Fed. Cir. 2009) ("We therefore hold that . . . an analysis of obviousness . . . may include recourse to logic, judgment,

and common sense available to the person of ordinary skill that do not necessarily require explication in any reference or expert opinion.").

476. Courts have sought to determine whether "a person of ordinary skill, before the time of invention and without knowledge of that invention, would have found the invention merely an easily predictable and achievable variation or combination of the prior art." *Rolls-Royce, PLC v. United Techs. Corp.*, 603 F.3d 1325, 1338 (Fed. Cir. 2010). If so, then the invention likely would have been obvious. *Id.* (citation omitted). "To preclude hindsight," the courts will take into account "evidence from before the time of the invention in the form of some teaching, suggestion, or even mere motivation . . . to make the variation or combination." *Id.* (citations omitted).

477. "[A] suggestion, teaching, or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather 'may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself.'" *Pfizer*, 480 F.3d at 1362 (Fed. Cir. 2007) (quoting *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006)).

478. "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." *Id.* "[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute." *Life Techs., Inc. v. Clontech Lab., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000); *see also Std. Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985) ("[O]ne should not go about determining obviousness under § 103 by inquiring into what patentees . . .

would have known or would likely have done"). The inquiry into whether prior art teachings would have rendered the claimed invention obvious to one of ordinary skill in the art, is, as a matter of law, "independent of the motivations that led the inventors to the claimed invention." *Life Techs.*, 224 F.3d at 1325.

479. "One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claim." *KSR*, 550 U.S. at 419-20; *see also Norgren Inc. v. ITC*, 699 F.3d 1317, 1324-26 (Fed. Cir. 2012) (affirming invalidity of claims under § 103 where the claimed invention solved known problems by the use of an obvious solution). Even more, the discovery of a problem does not always result in a patentable invention. *Norgren*, 699 F.3d at 1327. For instance, an alleged invention is obvious in view of "evidence of known problems and an obvious solution." *Id.* Where a claim "simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." *KSR*, 550 U.S. at 417 (quotation omitted).

480. "When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious. *KSR*, 550 U.S. at 421.

481. "When a work is available in one field, design incentives and other market forces can prompt variations of it, either in the same field or in another. If a person of ordinary skill in

the art can implement a predictable variation, and would see the benefit of doing so, § 103 likely bars its patentability. Moreover, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill." *KSR*, 550 at 401.

482. None of "the length, expense, [or] difficulty of the techniques used are dispositive since many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably 'routine' to one of ordinary skill in the art." *Pfizer*, 480 F.3d at 1367.

483. A "claim to a product does not become nonobvious simply because the patent specification provides a more comprehensive explication of the known relationships between the variables and the affected properties." *In re Applied Materials, Inc.*, 692 F.3d at 1297.

484. Even if a reference does not rise to the level of prior art, a court may consider it as motivation to combine. *See, e.g.*, *Lucent Techs., Inc. v. Gateway, Inc.*, 537 F. Supp. 2d 1095, 1102 (S.D. Cal. 2008) (*citing Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1337-38 (Fed. Cir. 2004)).

485. The motivation to combine inquiry is not limited to what products are forthcoming or currently available on the market, particularly given the lengthy FDA approval process. *Bayer*, 874 F.3d at 1324; *see also id.* at 1326 ("'Motivation to combine may be found in many different places and forms; it cannot be limited to those reasons the FDA sees fit to consider in approving drug applications.'") (quoting *Allergan*, 726 F.3d at 1292). "Obviousness does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art does not teach away." *Id.* at 1328 (emphasis in original).

486. The inherency doctrine discussed with regard to anticipation may also apply to an obvious claim. *Allergan*, 726 F.3d at 1294 n.1.

487. If the asserted prior-art references render the claim obvious, it does not matter who offered the explanation. *See Senju Pharm. Co., Ltd. v. Apotex, Inc.*, 717 F. Supp. 2d 404, 423-25 (D. Del. 2010) (finding that a patent claim may be invalidated by testimony from patentee's own expert admitting its obviousness). It is the Court's duty as arbiter of the public interest to extinguish the patent monopoly it if the evidence proffered by either side renders it invalid. *See U.S. v. Glaxo Group Ltd.*, 410 U.S. 52, 69 (1973) ("[T]here is a public interest favoring the judicial testing of patent validity. . . . For when a patent is invalid, the public parts with the monopoly grant for no return, the public has been imposed upon and the patent clause subverted.")

488. The Court finds that a POSA would have understood Fieser, Guillory, and Byrn 1994 to teach methods for crystallizing or recrystallizing from a single solvent or a mixture of solvents, including using fast cooling. *See Hospira*, 285 F. Supp. 3d at 783; DFF ¶ 1731. A POSA would have been motivated to combine the general disclosures of Fieser, Guillory, and Byrn 1994 with the '052 publication because the general disclosures would have provided useful guidance on how best to carry out a polymorph screen on the enantiomerically pure apremilast. DFF ¶¶ 1731-33.

489. Based on teachings of Fieser, Guillory, and Byrn 1994, a POSA would have been motivated to try at least fast and slow cooling rates in the procedure set forth in Example 2 of the '052 publication, and would have reasonably expected to succeed in producing enantiomerically pure apremilast in crystalline form. *See Hospira*, 285 F. Supp. 3d at 783; DFF ¶ 1733. Fast

cooling would inherently produce apremilast Form A crystals exhibiting the five peaks in claim 2 of the '283 patent when analyzed by XRPD. *See Allergan*, 726 F.3d at 1294 n.1; DFF ¶ 1733.

490. The '052 publication, in combination with Fieser, Guillory, and Byrn 1994 would have led a POSA to conduct a polymorph screen that would have resulted in crystalline apremilast Form A with a reasonable expectation of success. *See Hospira*, 285 F. Supp. 3d at 783; DFF ¶¶ 1735-39.

491. Based on teachings about the therapeutic utility of apremilast in the '052 publication, a POSA would have been motivated to formulate the enantiomerically pure apremilast Form A obtained from Example 2 into pharmaceutical compositions, and would have reasonably expected to succeed in those efforts, so claim 27 is obvious. *KSR*, 550 U.S. at 416; DFF ¶ 1734.

492. The preclinical tests in the '052 patent would have provided motivation to a POSA to conduct a polymorph screen on enantiomerically pure apremilast. A POSA would have been able to design the polymorph screen using ethanol, acetone, and mixtures thereof, and varying cooling rates, including fast cooling. DFF ¶ 1738. A POSA would have reasonably expected to succeed in recrystallizations based on Example 2 and that a POSA would have been able to determine the diffraction peaks of the resulting crystalline material. *KSR*, 550 U.S. at 416; DFF ¶ 1738.

3. Secondary Considerations/Objective Indicia Of Non-Obviousness.

493. As part of the obviousness analysis, courts must evaluate evidence that the patentee puts forward to show the existence of any "secondary considerations" or "objective indicia" of non-obviousness. *See KSR*, 550 U.S. at 406.

494. There are no secondary considerations of nonobviousness relating to the '283 patent. DFF ¶ 1740.

VII. The Asserted Claims Of The '541 Patent Are Invalid.

A. The Legal Standard.

495. Section 103 of the Patent Act "forbids issuance of a patent when 'the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.'" *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The court is to assess four considerations: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) objective indicia of non-obviousness. *See Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966).

496. The Supreme Court has instructed that engagement with the question of obviousness requires "an expansive and flexible approach" that requires "caution in granting a patent based on the combination of elements found in the prior art." *KSR*, 550 U.S. at 415.

497. "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. *If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability*." *Id.* at 417 (emphasis added). Put simply, "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* at 416. Thus, in examining obviousness, "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.* at 417.

498. Where, as here, the prior art is modified to reach the claimed result, the Federal Circuit has set forth a manner of analyzing obviousness claims according to two factors: "(1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the

prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *Warner Chilcott Co., LLC v. Teva Pharms. USA, Inc.*, 89 F. Supp. 3d 641, 674-75 (D.N.J. 2015) (quoting *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed. Cir. 2006)).

499. A suggestion to carry out the claimed process

> may come expressly from the references themselves. It may come from knowledge of those skilled in the art that certain references, or disclosures in the references, are known to be of special interest or importance in the particular field. It may also come from the nature of the problem to be solved, leading inventors to look to references relating to possible solutions to that problem.

Id. at 675 (quoting *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996)). "[T]he analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418.

500. The reasonable expectation of success factor does not require conclusive proof of success. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1331-32, 1333 (Fed. Cir. 2018) ("This court has long rejected a requirement of '[c]onclusive proof of efficacy' for obviousness.") (citing *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1364 (Fed. Cir. 2007); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364, 1367-68 (Fed. Cir. 2007)). Rather, it is "sufficient to show … 'an expectation,' in light of the totality of the prior art, that the new [composition] will have '*similar properties*' to the old." *Aventis Pharma*, 499 F.3d at 1301 (citation omitted).

B. The '541 Patent Claims And The Level Of Ordinary Skill In The Art.

501. The '541 patent is generally directed to method of treating a patient with psoriasis according in which apremilast is administered according to a dosing titration schedule as follows:

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
a.m.	10 mg	10 mg	10 mg	20 mg	20 mg	30 mg
p.m.		10 mg	20 mg	20 mg	30 mg	30 mg

502. In essence, the dose is titrated by adding 10 mg a day to the regimen until 60 mg is reached on Day 6.

503. A person of ordinary skill in the art with respect to the asserted claims of the '541 patent would be a physician specializing in dermatology or rheumatology, having an M.D., or a Ph.D. in pharmacology, biochemistry, or related discipline and significant clinical experience in one or both of these medical sub-specialties. DFF ¶ 1800. A POSA would have had access to and consulted with a multidisciplinary team of ordinarily skilled artisans in related and relevant disciplines such as pharmacology and chemistry. *Id.*

C. The Scope And Content Of The Prior Art.

504. In 2002, Amgen's predecessor, Celgene, filed the '536 patent, which contains a general disclosure of apremilast and its usefulness in treating psoriasis. While the '536 patent contains no clinical data establishing an effective dose for apremilast or demonstrating efficacy in treating psoriasis, it establishes that apremilast would be useful to treat psoriasis, and sets forth broad parameters for potential doses of apremilast.

505. The Papp article—the closest prior art—was published in 2012, in one of the premier medical journals in the world, The Lancet. DFF ¶¶ 1806-07. Papp is an article describing Phase II, dose ranging studies of apremilast in patients with psoriasis. All parties agree that Papp discloses an effective dose for apremilast of 60 mg a day, given twice a day in 30

mg doses ("30 mg BID"). DFF ¶¶ 1808, 1820. This is the "maintenance dose" meaning the dose the patient is to take for the period of treatment after the dose is titrated up. The parties further agree that Papp discloses that the 30 mg BID dose was the dose to be used in the Phase III clinical trials—the final set of safety and efficacy trials necessary for FDA approval. *Id.* Accordingly, the court finds that a POSA reading these disclosures in Papp would have understood that the 30 mg BID dose of apremilast was the most effective dose for treating psoriasis, showed the most promise, and was expected to be used as the maintenance dose. *Id.*

506. The parties also agree that Papp discloses that apremilast has dose dependent adverse events "meaning that if the dose increases, the likelihood of an event would increase too." DFF ¶¶ 1809 (quoting Dr. Alexis), 1821. Because of this dose dependent characteristic, doses in the Papp study were titrated up to the maintenance dose of 30 mg BID over a period of five days. Papp taught that this "dose titration can be used to mitigate adverse events" caused by apremilast. DFF ¶¶ 1809, 1822 (quoting Dr. Alexis). Dose titration is the common sense notion that patients should be given gradually increasing amounts of the drug so that they grow accustomed to the drug before the full maintenance dose is reached. In doing so, the side effects or adverse events associated with the drug can in many cases be reduced. *Id.* As with the maintenance dose, the parties do not dispute that Papp discloses a motivation for titrating the dose up to the 60 mg a day maintenance dose, and discloses that the titration in this study took place over a five-day period.

507. The parties dispute whether Papp discloses enough information from which a person of skill in the art could determine the specific dosing titration schedule used in the study. Both sides agree that the actual dosing schedule used in Papp is as follows:

	Day 1	Day 2	Day 3	Day 4	Day 5
a.m.	10 mg	10 mg	20 mg	20 mg	30 mg

p.m.	10 mg	10 mg	20 mg	20 mg	30 mg

508. Given the express disclosure in Papp of the 30 mg BID final dosage amount and the five-day titration schedule, and the other prior art relevant to apremilast dosing regimens, the Court finds that a person of skill in the art would know the remaining parameters of the Papp dosing regimen. The Court finds Dr. Gilmore's testimony credible on this matter.

509. As Dr. Gilmore testified, based on the description in Papp, a person of skill in the art would assume that the "enrollees would have incremental symmetric or same magnitude increases in dose per day, or per period of time, until the maximum dose is achieved on day 5," and that the dose increases would be of the same magnitude because that is "the most simplistic explanation" and "oftentimes the way [physicians] titrate doses of medication." DFF ¶¶ 1810-11. As she explained, unless the article said otherwise (and, here, it did not), a person of skill in the art would reasonably assume that the dose titration was step-wise equivalent over both the amounts increased and the intervals between the increases. DFF ¶ 1812. Dr. Gilmore testified that POSA would therefore understand that Papp started patients at 20 mg (10 mg BID) on day one and increased the dose by 20 mg a day every two days until the 60 mg daily maintenance dose was reached on day 5.

510. Other prior art available as of the 2014 effective filing date confirms the teachings of Papp regarding the dose titration schedule—in particular, the Pathan reference, which was another Phase II study funded by Celgene Corporation at the same time as Papp, investigating the efficacy and safety of apremilast in treating ankylosing spondylitis, an inflammatory condition involving the bones and the spine. DFF ¶ 1813.[2] Pathan teaches the same

[2] The Court finds that Defendants' use of Pathan as support for what a person of skill in the art would know about the Papp schedule was properly disclosed in Dr. Gilmore's expert report and declines Amgen's request to exclude this testimony.

maintenance dose of 30 mg BID as Papp, titration for dose dependent adverse events over a period of five days, just like Papp, and that patients "were started on apremilast 10 mg twice daily or placebo and the dose was titrated by 20 mg every 2 days until the maximum dose of 30 mg twice daily was achieved on day 5." DFF ¶ 1814. In other words, Pathan expressly discloses the same dosing titration schedule that was actually used in Papp, and confirms Dr. Gilmore's testimony about what a person of skill in the art would have determined was used in Papp. *Id.*

511. Although Pathan relates to a different disease state, both Dr. Gilmore and Dr. Alexis agree that this literature specifically dealing with apremilast would be directly relevant to a person of skill in the art. *Id.* *See, e.g.*, *Bayer Schering Pharma AG v. Barr Labs., Inc.*, Civ. Action No. 05-cv-2308 (PGS), 2008 WL 628592, at *31-32 (D.N.J. Mar. 3, 2008) (holding that prior art concerning closely related drug was relevant to what a POSA would find obvious in claimed formulation of drug); *see also KSR*, 550 U.S. at 420 ("Common sense teaches, however, that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle."). Accordingly, the court finds persuasive Dr. Gilmore's testimony that a person of skill in the art would have readily surmised the dosing titration schedule in Papp and that this dosing schedule is a fixed, one-size-fits-all dosing titration schedule. *KSR*, 550 U.S. at 418 ("[A] court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.").

512. Finally, Schett is another piece of prior art related to clinical studies on dosing of apremilast. Schett is a Phase II study regarding safety and efficacy of apremilast in psoriatic arthritis. The dosing in Schett did not go higher than 40 mg daily, so the court finds that it is not as close prior art as Papp but nevertheless provides useful information regarding apremilast

dosing. First, like Papp, Schett discloses a fixed titration schedule for apremilast. Importantly, Schett establishes that a 10 mg dose is an appropriate starting dose for titration. DFF ¶ 1817-18. It also establishes that dosing titration does not extend beyond eight days to arrive at the maintenance dose. DFF ¶ 1817-18, 1826. Thus, while it does not provide the final maintenance dose for psoriasis (Papp did), but instead only provides information about different dosing regimens for psoriatic arthritis, Schett provides useful information to a person of skill in the art regarding a starting point for titration—specifically, how low a person of skill in the art can go to start titrating the dose and the longest titration schedule tested. *Id.*

513. These three disclosures, Papp, Pathan, and Schett, are the only disclosures in the art that provide actual clinical data regarding efficacy and safety of apremilast in patients with disease, and would indisputably be the most relevant information to a person of skill in the art determining how to start and maintain a psoriasis patient on apremilast. DFF ¶¶ 1806, 1826

D. Motivation To Modify Papp.

1. A Person Of Skill Would Be Motivated To Modify The Papp Schedule To The Claimed Dosing Titration Schedule.

514. "One of the ways in which a patents' subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims." *KSR*, 550 U.S. at 419-20. Following this instruction, the Federal Circuit has found drug dosing schedules obvious when they effect minor changes to dosing schedules disclosed in the art to mitigate side effects or adverse events.

515. For example, in *Cubist Pharmaceuticals, Inc. v. Hospira, Inc.*, the Federal Circuit affirmed a district court's finding that a claimed dosing schedule, administering daptomycin at a specific dose either once daily for some asserted claims or once every two days for others, was rendered obvious by a disclosure of laboratory studies suggesting that the claimed dosage levels

would be effective and stating that "daptomycin's effectiveness is concentration-dependent, which suggests that less frequent and more concentrated treatments would be more effective than smaller doses of the drug administered at more frequent intervals." 805 F.3d 1112, 1123-25 (Fed. Cir. 2015).

516. Similarly, in *Acorda*, the Federal Circuit upheld a finding of obviousness for a sustained release dose of 4-AP at 10 mg, twice a day despite the art teaching that the drug could be titrated to avoid adverse events and administered at higher doses, and rejected the patent holder's argument that a person of skill in the art would not be motivated to pursue a stable dosing regimen, given prior art titration. 903 F.3d at 1330-31. The court reasoned that the art supported a starting dose of 10 mg, twice a day, and taught that higher doses might produce more adverse events. *Id.*

517. In *Hoffmann-La Roche*, the Federal Circuit upheld a District Court finding of obviousness, holding that a patent claiming 150 mg dose administered once a month was obvious in view of art teaching that a person could scale up a known effective dose of about 150 mg over a specific period of time from a short-interval regimen to achieve the same with a long-interval regimen. 748 F.3d at 1331-32. The prior art study disclosed a total dose useful for treating the claimed disease and that this total dose could be used as a rule of thumb in order to decide how to scale intermittent dosing, but did not teach any specific intermittent dosing schedule. Nevertheless, the Federal Circuit concluded that the District Court did not err in finding it reasonable to expect the claimed dosing regimen of once monthly dosing of 150 mg to work based on a disclosure of 5 mg daily dosing. *Id.* at 1333.

518. Similarly, the Federal Circuit in *Teva Pharms. USA Inc. v. Sandoz, Inc.*, affirmed a District Court decision holding that a patent claiming dosing of 40 mg every three days was

rendered obvious by prior art disclosure of dose of 40 mg every other day. 906 F.3d 1013, 1025 (Fed. Cir. 2018). There, the court found that the prior art disclosed that patients would want to avoid extra injections and the art suggested that increasing the dosing interval would not affect effectiveness. *Id.* at 1025.

519. Here, Amgen claims as inventive the same kinds of minor alterations of prior art regimens that the Federal Circuit has ruled obvious in the past. The Papp reference itself provides the motivation for arriving at the dose titration schedule claimed in the '541 patent. Papp discloses the maintenance dose of 30 mg BID and teaches that this dose should be titrated over a short period of time—less than a week—in order to mitigate adverse events. This relatively short titration is also supported by Schett. DFF ¶¶ 1817-18, 1826.

520. Papp also discloses data regarding adverse events. Specifically, a significant number of patients in Papp in the 30 mg BID treatment arm still experienced treatment-related adverse events despite the 5-day dose titration, particularly during the first few weeks of treatment. DFF ¶¶ 1815, 1823. The Court finds Dr. Gilmore's testimony regarding the motivation to modify Papp credible. Dr. Gilmore testified that these "percentage of adverse events [disclosed in Papp], which are not pleasant types of adverse events, are quite significant and would indicate that there was room for optimization of the titration schedule, with the understanding that half of these events occur within the first two weeks of treatment." DFF ¶ 1823. A person of skill in the art would therefore have been motivated to modestly alter the fixed dosing titration schedule in Papp to further improve the tolerability of apremilast in psoriasis patients. *Id.*

521. The Court finds that a person of skill in the art would have been motivated to start at the lowest available dose—10 mg a day—instead of 20 mg a day as used in Papp, and to slow

the dose titration schedule from Papp to further ameliorate adverse events. DFF ¶ 1824. Thus, as Dr. Gilmore testified, a person of skill in the art would have been motivated to start with 10 mg of apremilast on the first day of treatment and increase the dose by 10 mg per day until reaching the target dose of 30 mg twice daily, or 60 mg per day, on day 6. DFF ¶ 1825. This minor adjustment to the dosing schedule would result in a slight slower titration of six days rather than five, while not sacrificing potential effectiveness. As Dr. Gilmore explained, it is like taking one step at a time rather than two steps at a time, which is an obvious way to avoid physical strain. This minor adjustment results in the same dosing schedule claimed in claims 2, 19, and 21 of the '541 patent and would be obvious in view of Papp's disclosures. DFF ¶¶ 1825, 1832-35. Indeed, this case is similar to *Hoffman La Roche* and *Teva*, in that the art here, as there, teaches the general principles from which a person of skill in the art could find a reasonable dosing schedule, even though the art does not expressly teach the claimed dosing schedule. *See Hoffmann La-Roche*, 748 F.3d at 1331-33; *Teva*, 906 F.3d at 1026, *affirming Copaxone*, 2017 WL 401943, at *15-16.

522. Moreover, the Court finds that even if Dr. Alexis were correct that Papp does not disclose the specific dosing titration schedule used and a person of skill in the art would be unable to make reasonable inferences from the Papp disclosure, a person of skill in the art had the ability to optimize the dosing titration schedule as a routine matter. Dr. Alexis conceded this fact on cross examination: "Q. …It's within the skill of a doctor like you to individually titrate a dose for a patient that's presented to you with psoriasis; is that right? A. Yes. … [dose titration] would be a routine aspect of treating psoriasis patients with any of those drugs that require dose titration." DFF ¶¶ 1832, 1835 (quoting Dr. Alexis); *see also* DFF ¶¶ 1832-35 (Dr. Gilmore also testified this is no more than routine optimization).) As the Supreme Court has instructed, "[i]f a

person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *KSR*, 550 U.S. at 417. The disclosure in Papp of the 30 mg BID maintenance dose titrated at 20 mg increases every two days arriving at a five-day titration schedule would make a six-day titration schedule at 10 mg a day increases, as claimed, an exercise of routine optimization that was well within the skill of a clinician; in simpler terms, the claimed dosing schedule is a predictable variation from Papp. As this Court has held, "[m]erely 'optimizing' a variable is obvious unless the result is 'unexpectedly good.'" *Warner Chilcott*, 89 F. Supp. 3d at 673-74 ("[N]o precise ratio of EDTA to other ingredients is required to achieve its purpose of blocking calcium after a meal without harming the intestinal tight junctions."). Amgen produced no evidence of unexpected results from the claimed dosing titration schedule. *See AstraZeneca LP v. Breath Ltd.*, No. 2015-1335, 603 Fed. Appx. 999, 1002 (Fed. Cir. May 7, 2015) ("[A]lthough each sterilization method had known disadvantages, a skilled artisan 'had within her toolbox several methods to address them.'").

523. The Court concludes that the person of skill in the art would be motivated to modify Papp and arrive at the claimed dosing titration schedule from the '541 patent.

2. Amgen's Rebuttal.

524. Amgen raises several arguments regarding motivation, but none are persuasive because they ignore what the art taught specifically about Apremilast dosing regimens and instead amount to unsupported speculation about the number of options POSA theoretically could have pursued.

525. First, Amgen makes much of the "fixed, one-size-fits-all" dosing titration schedule claimed in the '541 patent, which it contends defies the conventional wisdom of individualized dosing titration. Alexis Tr. 1765:15-23. But the most relevant apremilast prior art, namely Papp, Pathan and Schett, all teach that "fixed, one-size-fits-all" dosing titration schedules

should be used with apremilast. DFF ¶¶ 1811-14, 1817-18. The only apremilast art that Amgen relies on for this argument is the '536 patent, which provides some limited useful information about apremilast dosing and uses, but unlike Papp, Pathan and Schett, contains no clinical data, and precedes those articles by a decade. Thus, the Court concludes that the fixed, one-size-fits-all dosing titration schedule was obvious in view of the prior art and would not constitute a counter intuitive move given the art's teachings.

526. Second, Amgen argues that a person of skill in the art theoretically could have pursued higher doses than the 30 mg BID dose. Alexis Tr. 1789:12-1790:19, 1795:5-1796:14. But, the prior art contains no such teaching and Amgen's argument is based solely on Dr. Alexis' testimony, which was unsupported by reference to any prior art reference. The Court does not credit Dr. Alexis's testimony that a person of skill in the art would be motivated to use a dose higher than 60 mg a day. The prior art relevant to apremilast teaches that the 30mg BID dose would work to treat psoriasis, and Dr. Alexis admitted this fact on cross examination. DFF ¶ 1836 (Dr. Alexis admits a POSA would expect the claimed dosing regimen to work).)

527. Third, Amgen argues that a person of skill in the art would be motivated to pursue a dose titration schedule significantly longer than anything disclosed in the prior art. Alexis Tr. 1777:11-19. This assertion, too, is based not on any actual extended dose titration schedule used in the art, but solely on Dr. Alexis's testimony, which the Court does not find persuasive. The prior art disclosed only very short titration schedules ranging from five to eight days, and nothing longer. DFF ¶ 1826. There is no art to support Amgen's contention that a person of skill in the art would have considered numerous other possibilities. That this type of alteration of a prior art regimen is obvious. *See Copaxone*, 2017 WL 401943, at *19 ("It is therefore not farfetched to assume a person of ordinary skill in the art would have been motivated to pursue a regimen close

to the ones already known to be safe and effective."). Dr. Gilmore's real-world experience confirms this point. Dr. Gilmore started with the claimed dosing titration schedule of the '541 patent, fully expecting it to work, just as Papp taught that a similar short schedule would work. Well after the 2014 priority date for the '541 patent, and only after a few years writing prescriptions for apremilast, Dr. Gilmore determined that the schedule needed adjustment.

528. Fourth, Amgen argues that POSA would have believed that the short titration schedule in Papp was sufficient and that a person of skill in the art would not be motivated to change it. Alexis Tr. 1782:9-16. But, it is black letter law that the fact that there were possible options beyond a short duration titration schedule does not render this particular regimen not obvious. *Acorda*, 903 F.3d at 1330-31 (holding that prior art teaching titrated dosing scheme to avoid adverse events did not render stable dosing scheme at low doses unobvious); *see also PAR Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014) (Obviousness "does not require that the motivation be the *best* option, only that it be a *suitable* option.") (emphasis in original); *Bayer*, 874 F.3d at 1329 ("While a skilled artisan may have preferred a delayed-release formulation over the claimed immediate-release formulation, 'that the prior art as a whole suggests the desirability of a particular combination need not be supported by a finding that the prior art suggests that the combination claimed . . . is the preferred, or most desirable, combination.'") (quoting *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004)); *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (Even if "better alternatives exist in the prior art[,] [that] does not mean that an inferior combination is inapt for obviousness purposes."). Amgen did not offer any evidence teaching that the claimed dosing schedule would not be a suitable option. On the contrary, the evidence demonstrates the opposite: a short titration schedule was supported by the Papp and Schett disclosures and Papp also disclosed that there was room for improvement. As

Dr. Gilmore explained, Papp disclosed that patients were still experiencing adverse events that might be further reduced with a slightly longer and slower titration.

529. Moreover, this Court does not find Dr. Alexis's testimony on this topic credible, as it is directly contradicted by Amgen's *other* argument that a person of skill, looking at Papp, would want a very long titration schedule. Similarly, Dr. Alexis simultaneously argues that the claimed dosing titration schedule is a "notable difference" in dosing titration from Papp and that the two schedules are "completely different," but "if you simply extend that five-day titration schedule to six days," the change in the schedule would have been so slight that POSA would not have expected "a major clinically meaningful improvement in tolerability," and therefore would have wanted a significantly longer dosing schedule. DFF ¶¶ 1834, 1837. Clearly, a one-day difference in a dosing schedule cannot be both significant and insignificant and the Court does not credit Dr. Alexis's testimony here. Rather, the Court finds that the claimed regimen is a merely minor adjustment of the prior art regimen that would have been obvious to a person of skill in the art.

530. Finally, the Court gives no weight to Amgen's speculation that there could be 70,000 different permutations with a six day schedule. When the art directs a person of skill to an obvious claimed schedule, as for instance in *Hoffmann La-Roche* and *Teva*, that is sufficient to establish obviousness, regardless of theoretical possibilities. *See Hoffmann La-Roche*, 748 F.3d at 1331-33; *Teva*, 906 F.3d at 1025. As an initial matter, there is no evidence in the record that most of these 70,000 alleged permutations would even be reasonable dosing titration schedules.[3]

[3] There is reason to think most of these schedules are patently unreasonable. For example, given Dr. Alexis's assumptions, the permutations would include a schedule in which the patient is administered 10 mg a day for five days and 60 mg on day 6, which is given equal weight in Amgen's analysis to the claimed 10 mg a day increases up to six days. Given the absence of any analysis of a schedule as or more reasonable than the claimed schedule, the Court affords this

But, more importantly, if a person of skill followed what the art legitimately discloses, two of Dr. Alexis's main assumptions are untenable. First, Dr. Alexis assumes there are not three available doses (10, 20, or 30 mg), but six, including 5, 15, and 25 mg doses. But, there is no data in the art showing that 5 mg, 15 mg, or 25 mg are acceptable doses to administer to a patient. DFF ¶¶ 1827, 1829. Rather, the art only describes 10, 20, and 30 mg doses administered to patients.[4] Second, given the disclosure in Papp, the closest prior art, the Court finds that an assumption of evenly titrated doses is more warranted than Dr. Alexis's assumption of unevenly titrated doses. Correcting for just those two assumptions reduces Dr. Alexis' possible permutations to no more than 18. And had Dr. Alexis actually specified any of those 18 options, undoubtedly some would be facially unreasonable.

531. Most importantly, however, none of these theoretical doses, disconnected from any actual prior art dosing, makes the claimed alteration from starting at 20 mg and increasing by 20 mg every two days to starting at 10 mg and increasing by 10 mg a day, as claimed in the '541 patent, any less obvious. *Teva*, 906 F.3d at 1025 ("Here, the prior art focused on two critical variables, dose size and injection frequency, and provided clear direction as to choices likely to be successful in reducing adverse side effects and increasing patient adherence."). The Court concludes that it is obvious to go from two steps at a time, per Papp, to one step at a time, per the claimed dosing titration schedule. The Court rejects Amgen's arguments, based on speculation unmoored from the teachings of the prior art.

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argument no weight.

[4] The Court concludes that Dr. Alexis's argument that the '536 patent and WO '102 application disclose that tablets can contain 5 mg is irrelevant. There is no clinical data showing that any multiples of 5 mg other than 10, 20, or 30 mg, were ever administered to a patient. (FOF ¶¶ __.)

E. A Person Of Skill In The Art Would Reasonably Expect Success In Treating Psoriasis With The Claimed Dosing Titration Schedule.

532. Finally, the Court concludes that there was a reasonable expectation that the claimed titration schedule would succeed. The asserted claims are directed to treating patients with psoriasis, only, and say nothing about reducing adverse events: "Q. And [asserted claim 2] doesn't say anything about reducing adverse events in this claim, does it? A. It only speaks to the method." DFF ¶ 100 (quoting Dr. Alexis).) As Dr. Gilmore explained, given Papp's disclosure that 60 mg a day treated patients' psoriasis using a dose titration schedule of five days, a person of skill in the art also would reasonably expect a six-day dose titration schedule, like the one claimed, to treat psoriasis. DFF ¶ 1836. And Dr. Alexis agreed: "The efficacy of the maintenance dose of 60 milligrams a day, we are informed of that efficacy by the Papp 2012 article. If the titration schedule is extended by one day, … I personally would not have the expectation that it would not have efficacy." *Id.* This admission is dispositive: a person of skill in the art would reasonably expect success and therefore the asserted claims are invalid as obvious. *Acorda*, 903 F.3d at 1329-30 (holding that reasonable expectation of success is directed to what is claimed, not to unclaimed effects).

533. Amgen attempts two arguments to get around Dr. Alexis's concession: First, Amgen argues that a person of skill in the art would not reasonably expect the six-day titration schedule to mitigate adverse events. Dkt. No. 399 (Amgen's Pretrial Brief) at 120. But, again, reducing adverse events is not what is claimed in the '541 patent, so this argument is irrelevant. *Acorda*, 903 F.3d at 1329-30. It is also untrue: Papp expressly teaches that titrating the dose will reduce adverse events, and Dr. Alexis agrees that if a patient is given less drug, e.g., 10 mg versus 20 mg, a person of skill in the art would expect fewer adverse events, just as Papp teaches. DFF ¶ 1837.

534. Second, Amgen suggests that a person of skill in the art would be required to test every single one of the over 70,000 permutations to which Dr. Alexis testified, before having a reasonable expectation of success. If Amgen were correct that expert claims that POSA would have to test thousands of possible regimens was sufficient to defeat obviousness, no dosing patent would ever be obvious. But, it is black letter law that testing is not required to show reasonable expectation of success and that dosing patents frequently are found invalid for obviousness.

535. In fact, the Federal Circuit "has long rejected a requirement of '[c]onclusive proof of efficacy' for obviousness." *Acorda*, 903 F.3d at 1333 (holding that a person of skill in the art would reasonably expect effectiveness "in the absence of publications showing a statistically significant difference" in placebo-controlled trials). "Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffmann-La Roche*, 748 F.3d at 1331 (holding that prior art testing showing improvement at certain doses in surrogate for claimed treatment established reasonable expectation of success of once monthly dosing schedule without any clinical efficacy testing for claimed dosing schedule); *accord Cubist Pharms*, 805 F.3d at 1124 (holding that prior art disclosure of laboratory, non-clinical testing showing claimed dose range to be effective was sufficient to establish reasonable expectation of success in treating patients at that dose); *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1364 (Fed. Cir. 2008); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364, 1367-68 (Fed. Cir. 2007); *AstraZeneca*, 603 Fed. Appx. at 1002 ("AstraZeneca mistakes the test for obviousness. Obviousness requires a showing that 'a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art.' … To meet this standard 'only a reasonable expectation of success, not a guarantee, is

needed.'"); *Warner Chilcott*, 89 F. Supp. 3d at 674 ("The absence of food effect studies documenting the relative effectiveness of other doses of EDTA does not diminish the persuasiveness of the expert testimony."). Dr. Gilmore and Dr. Alexis agree: a person of skill in the art would reasonably expect the claimed six-day dosing titration schedule to work, given the disclosure in Papp that the five-day dosing titration schedule worked.

536. To summarize, there was a motivation to modify Papp by starting at a lower dose of 10 mg a day and increasing by 10 mg every day rather than 20 mg every two days, which extends titration from five-day titration to six-day titration. There was a reasonable expectation that this six-day titration schedule would effectively treat psoriasis. There are no objective indicia of non-obviousness. Therefore, the Court holds that the asserted claims of the '541 patent are invalid as obvious under 35 U.S.C. § 103.

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CERTIFICATION OF SERVICE

The undersigned attorney certifies that a copy of the foregoing **DEFENDANTS' PROPOSED CONCLUSIONS OF LAW** was served by notice of electronic filing on the 8th day of July 2021, upon all counsel of record.

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